This transcript has not been edited or corrected, but appears as received from the commercial transcribing service; the Food and Drug Administration makes no representation as to its accuracy.

UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

- - -

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

- - -

MEETING

- - -

WEDNESDAY, JULY 29, 1998

21121 '98 AUG 31 P4:01

The Advisory Committee met in Versailles Rooms I and II, Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:30 a.m., Eric Brass, M.D., PhD, Acting Chair, presiding.

PRESENT:

ERIC P. BRASS, MD, PhD, Acting Chair
RHONDA STOVER, R.Ph, Executive Secretary
MARY A. KODA-KIMBLE, PharmD, Member
LYNN McKINLEY-GRANT, MD, Member
GEORGE A. BLEWITT, MD, Industry Representative
MARIAN MELISH, MD, Anti-Infective Representative
ROSELYN RICE, MD, Anti-Infective Representative
RALPH B. D'AGOSTINO, PhD, SGE, Consultant
THEODORE G. TONG, PharmD, Consultant
EDWIN E. GILLIAM, MSN, PhD, CFNP, Guest
JOHN P. GUZEWICH, MPH, Guest

PRESENT: (continued)

EDWARD P. KRENZELOK, Pharm D, Guest
ELAINE L. LARSON, PhD, RN, FAAN, Guest
DENNIS G. MAKI, MD, Guest
RICHARD A. NEILL, MD, Guest

LINDA KATZ, MD, MPH, FDA Representative
DEBBIE LUMPKINS, BS, FDA Representative

Public Comment:

PAUL MARSHALL
SYED A. SATTAR, PhD
ABDUL B. ZAFAR, MBBS, MPH

I N D E X

1 **P R O C E E D I N G S**

2 Time: 8:31 a.m.

3 CHAIRMAN BRASS: Thank you and good
4 morning. On behalf of the Nonprescription Drugs
5 Advisory Committee, I'm Eric Brass, and I'll be
6 chairing this morning's meeting.

7 I'd like to turn the microphone over to
8 Rhonda Stover for the conflict of interest statement.

9 MS. STOVER: The following announcement
10 addresses the issue of conflict of interest with
11 regard to this meeting and is made a part of the
12 record to preclude even the appearance of such at this
13 meeting.

14 Based on submitted agenda and information
15 provided by the participants, the agency has
16 determined that all reported interests in firms
17 regulated by the Center for Drug Evaluation and
18 Research present no potential for a conflict of
19 interest at this meeting.

20 With respect to invited guests, there are
21 reported interests with respect to the firms that make
22 health care antiseptics drug products that we believe

should be made public to allow the participants to objectively evaluate their comments.

Dr. Edward P. Krenzelok would like to disclose that he is the Director of the Pittsburgh Poison Center. The Center responds to poisoning and medical emergency inquiries as the corporate poison center for Colgate U.S. and its subsidiaries.

Dr. Elaine Larson would like to disclose that she is an investigator on 3M Corporation's study of skin flora and surgical scrubs.

Dr. Dennis Maki would like to disclose that he has grants from Becton-Dickinson/Deseret and 3M Company.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any

firm whose products they may wish to comment upon.

Thank you.

CHAIRMAN BRASS: We have an unusual composition at the front table this morning, and perhaps we can go around the room and introduce this morning's participants. I'll remind everybody, both at the table and other speakers, to please always use the microphones, and bring the microphone close to your mouth when talking, so that the transcriptionist can capture all your contributions.

We can start at the end of the table.

DR. NEILL: My name is Richard Neill. I'm a family physician and faculty member at the University of Pennsylvania in the Department of Family Practice and Community Medicine.

DR. KRENZELOK: I'm Ed Krenzelok. I'm Director of the Pittsburgh Poison Center. I'm a professor of pharmacy and pediatrics at the University of Pittsburgh, and currently President of the American Academy of Clinical Toxicology.

DR. GILLIAM: I'm Eddie Gilliam. I'm a Certified Family Nurse Practitioner with University

Physicians in Tucson, Arizona.

DR. TONG: Good morning. I'm Ted Tong. I'm a professor of pharmacology, toxicology and pharmacy practices at the University of Arizona in Tucson, Arizona, and I'm a consultant to the Nonprescription Drug Advisory Committee.

DR. D'AGOSTINO: I'm Ralph D'Agostino from Boston University, biostatistician and consultant.

DR. BLEWITT: I'm George Blewitt, industry representative to the Nonprescription Drugs Advisory Committee.

DR. McKINLEY-GRANT: I'm Lynn McKinley-Grant. I'm a dermatologist at the Washington Hospital Center and clinical associate professor at George Washington University and a member of the Nonprescription Drug Advisory Committee.

DR. KODA-KIMBLE: I'm Mary Ann Koda-Kimble, professor of clinical pharmacy at the University of California at San Francisco.

CHAIRMAN BRASS: I'm Eric Brass, Chair of the Department of Medicine, Harbor-UCLA Medical Center.

MS. STOVER: Rhonda Stover, FDA, Acting Executive Secretary for this committee.

DR. RICE: Good morning. Roselyn Rice, Regional Medical Director for Quality Management, Cigna HealthCare, consultant, anti-infectives for the FDA.

DR. MAKI: I'm Dennis Maki, Professor of Medicine at the University of Wisconsin and a specialist in infectious disease and critical care medicine.

DR. LARSON: Elaine Larson, Dean, Georgetown University, School of Nursing.

MS. LUMPKINS: Debbie Lumpkins, regulatory review microbiologist for the Division of OTC Drug Products.

DR. KATZ: I'm Linda Katz, Deputy Director of the Division of Over-the-Counter Drug Products.

CHAIRMAN BRASS: And Dr. Katz will be making some opening remarks on behalf of the FDA.

DR. KATZ: I'd like to welcome everyone this morning to our NDAC meeting, and I'd like to especially thank Dr. Brass, who has agreed to be our

Acting Chair or this committee, and also to thank all of those invited guests who have agreed to participate this morning.

The discussion this morning is really to focus on the effectiveness testing of final formulations for the over-the-counter health care antiseptic products. Today's discussion will, hopefully, be very lively, going through different kinds of performance testing measures and issues related to final formulation testing.

What we are hoping is that today's meeting will actually be a discussion, not just from around the table, but we also will invite those in the audience who may feel that they have information to contribute as well and may also not have been invited to be speakers to join in with some of the conversation and discussion, so that we can gain the most information that we can about how to go about final formulation testing.

Thank you.

CHAIRMAN BRASS: Thank you, and I think Debbie Lumpkins has some additional opening remarks.

MS. LUMPKINS: Good morning. Today's discussion will focus on what constitutes an appropriate demonstration of a topical antimocrobial's ability to meet certain performance expectations.

To set the stage for today's discussion, I'd like to provide some background on the scope of the products under discussion and give you an example of a currently proposed performance expectations and testing for a topical antimicrobial product.

The scope of OTC antimicrobials under discussion today encompasses wash products that are used from everyone from food handlers to health care professionals in a variety of situations.

The topical antimicrobial drug products being discussed are currently undergoing evaluation as part of the OTC drug review. Over the course of the review, a number of performance expectations have been defined for these products.

In general, each drug product category is defined by its particular performance expectations. The majority of performance expectations have been associated with the antimicrobial activity of the

product, and are: The speed of antimicrobial activity; the spectrum of its activity; the persistence of its effect; and the effectiveness of the product against resident versus transient microorganisms. However, not all of the performance expectations that have been proposed for these products relate to antimicrobial activity.

A low potential for irritation has also been proposed as a performance expectation.

As an example, a health care personnel hand wash is defined as: An antiseptic preparation designed for frequent use. It reduces the number of transient microorganisms on intact skin to an initial baseline level after adequate washing, rinsing and drying. It is broad spectrum, fast acting and, if possible, persistent.

In lieu of clinical testing of such products, currently proposed testing focuses on whether or not a health care personnel hand wash is able to demonstrate that it has the previously defined antimicrobial attributes through in vivo and in vitro testing.

This testing relies on microbial reductions as surrogate markers for clinical effectiveness. The demonstration of a low potential for irritation is not currently required.

So continuing with the health care personnel hand wash example, it is currently proposed that a product of this type demonstrate that it is broad spectrum by measuring the minimum inhibitory concentration of the product against an array of laboratory strains and fresh clinical isolates of bacteria associated with nosocomial infection.

The proposed definition is specific to professional use products like health care personnel hand washes, and it has been proposed that products used by consumers or food handlers have a different definition of broad spectrum to demonstrate that a product is fast acting, an in vitro time kill study delineating the kinetics of the antimicrobial activity. That is, the kill rate has been proposed.

To demonstrate activity against resident versus transient bacteria, an in vivo hand wash trial conducted using the product's label directions for use

is currently proposed. Activity against transient bacteria is demonstrated by the product's ability to reduce the number of marker organisms from artificially contaminated hands.

In order for a health care personnel hand wash to be considered effective, it must demonstrate a 2 log 10 reduction within five minutes after the first wash and a 3 log 10 reduction within five minutes after the tenth.

Persistence is an optional characteristic for health care personnel hand washes, and such products are not currently required to demonstrate persistence of effect. For these products for which persistence is a required performance expectation, persistence is demonstrated by the results of an in vivo test.

To demonstrate persistence, bacterial counts on the hands cannot exceed baseline counts for six hours.

Even though the example that I've given you today is specifically for health care personnel hand wash, it is illustrative of the general

characteristics for which all proposed testing for the categories under the review are.

These general characteristics are: That they relate to the antimicrobial expectations of the product; they involve both in vitro and in vivo testing; and they use surrogate markers for demonstration of effectiveness.

Today we'll hear from a variety of perspectives on this issue. As you listen to today's presentations, please keep in mind the following discussion points. I've paraphrased these for the sake of the slide.

In general terms, what is the appropriate test or tests for the previously discussed performance expectation -- that is, broad spectrum, fast acting, resident versus transient, and low irritation potential?

Also, should these testing requirements be based on the intended use of the product and, if so, how?

As Dr. Katz said, we're looking forward to a lively discussion today, and perhaps even a

reevaluation of the currently proposed way of demonstrating the performance characteristics of these products.

If there are no questions, I'm done.

CHAIRMAN BRASS: Are there any questions from the panel? Thank you.

Our first series of discussions will focus on performance expectations and testing requirements for antimicrobial wash products. While we would like there to be a lively discussion, I think, unless there is an urgent point of clarification, each presenter should be allowed to finish their individual talk, and then we will look for questions after each.

The first speaker will be Michael J. Dolan, Vice President of Gojo Industries, who will be speaking on performance expectations, attributes and indications.

MR. DOLAN: Yes. Good morning. Thank you, Mr. Speaker.

I was going to entitle the talk "A celebration of the fourth anniversary of the 1994 TFM," but we thought better of it, and changed it to

performance expectations and testing requirements for antimicrobial wash products.

As you mentioned, I'm Mike Dolan. I'm with Gojo Industries. Just for some background, we've been in business about 50 years. We develop and sell a variety of skin care products, primarily for occupational uses, which include a number of topical antimicrobials, both of OTC type as well as new drug type.

The specific topic today is topical antimicrobial products. I thought we would give just a brief view of what we mean by these products, for those of you who are not real familiar with them.

These are basically products that are sold today over-the-counter or nonprescription. The ones of specific interest today are covered by monograph process. The last issued monograph was a tentative final proposed rule in 1994.

The topic of today is primarily the products covered by that monograph, although we will make reference in some of our presentations to some new drug products, because they illustrate certain

points we want to make about the category of topical antimicrobials.

These include a number of product types, such as hand washes, body washes, rubs, in a variety of physical forms. These include bar soaps, for example, liquid soaps, hand gels, dips, sprays, a number of different product types; but all these are typically used in a skin antisepsis type situation.

The specific topics, as we understand them and will address today, are the questions before the panel. One is the performance expectations for the antimicrobial antiseptic drug products. The second one is appropriate testing for various performance characteristics that achieve these performance expectations and, finally, should the requirements be based on intended use.

Just a real brief history of how we got to where we are today. The original monograph proceedings go back quite a ways. In September 1974 there was a panel recommendation in terms of topical antimicrobials that included seven categories of products, ranging from the antimicrobial soaps to

surgical scrubs.

This resulted in a tentative final or proposed rule in 1978, which included those seven categories, and made recommendations about them.

Several of these were separated out, four through six, in the 1991 first aid monograph. So what we have now is a segregation of categories where some of these products disappeared into a separate monograph area and are covered there, the final monograph then being a tentative final that we're discussing today in 1994, which rolled over health care personnel hand wash, but not included the topic of antiseptic hand wash as an alternate statement of identify, as well as health care personnel hand wash, carried over surgical scrub and preoperative skin prep, but also contained a request for information on food handling antiseptic products.

So we will deal with these in certain ways today also. So the monograph today, as it's proposed, is significantly different than where the panel started where the initial monograph in the area came out, and we'd like to address those differences,

because we think there are significant issues there.

We have just a few key messages that we'd like to convey today. The first is that the health care continuum model that we developed as a response to the 1994 TFM, we believe, is still a very viable, useful frame of reference to consider when using -- upon applying regulations to the health care antiseptic products.

The model -- I will go into very little detail today, because you have all received background material on it. I notice some of the panel members who attended the symposium last year in Washington that dealt specifically with the ACCM model. I know a number of the people in the audience are familiar with it. So we will not go into much detail. We'll just summarize a couple of points about HCCM.

Our second message is that we believe there are clinical benefits associated with the full range of antimicrobial wash products. There are health outcomes in terms of infection risk reduction that can be attributed to all of these products across the full continuum.

We will use examples of those outcome studies and data, and link them to test methodologies to show the connections and disconnections between the health outcomes that the products are to achieve in terms of performance and the testing methodologies that establish the attributes that result in that performance.

In answer to the second question before the panel, should the situational factors for the intended use direct the performance expectations assessing the requirements, our answer is absolutely yes, and we will show data why we think that is true.

Finally and perhaps most significantly, we have significant concerns and issues with the proposed rule as issued. In fact, if it were to issue today as written, a number of benchmark new drug products, gold standards for this type of product categories, would not meet the monograph criteria.

We will give specific examples of this later. We'll also go into details of methodology where we have a number of issues. We believe a lot of work is needed to finish this area.

We will specifically deal in four areas with four different speakers. I will cover performance expectations from an attribute and indication standpoint. I'll reinforce some of the information that Debbie just presented.

Bruce Keswick of Proctor and Gamble will talk about some microorganism transmission data. This is new data that's not been published. We think it's germane to the topic.

We'll also talk about risk modeling and its application to other antimicrobial products and risk reduction, and finally Rhonda Jones will finish with a performance expectation conversation about linking clinical outcome data with laboratory test methodology and the implications of this to the regulatory process.

We go back to the health care continuum model for a minute, which was our starting point. This is based on a very simple fact that bacteria are ubiquitous.

Just as a side comment, let me note that the TFM specifically deals only with bacteria. It

does not deal with viruses. I believe you'll see some viral data today.

Virus data informs us about antiseptic products and how they work, but it is specifically excluded at this point from a monograph proceedings on topical antimicrobials.

So we need to keep that clear in our heads. We're not talking about proposed labelling and indications in regards to viruses, and viral data is interesting, and it tells us something about how these products work and how we should consider them.

So in response to the fact that bacteria are ubiquitous, we believe that there are a number of situations where bacteria become pathogenic. This proposes a risk of infection and diseases, and that in these situations, which are defined by the specific situation, the use of antimicrobial products can reduce that risk of infection.

That is, plain and simple, the benefit and the thinking behind the HCCM proposal. It says you look at the category or the situation that you're involved in. That determines the type of requirements

you want from an antiseptic product.

This then should tell you what kind of test methodology you want to use to substantiate that that product does, in fact, meet those performance expectations. That's the logic of the HCCM. That is basically the story we'll tell today.

Now we agree pretty much on what the main performance attributes of antimicrobial products should be. They should be judged on their speed of action, which typically is rapid but not necessarily.

For example, in a health care personnel hand wash setting you want very rapid disinfection of the hands before handling a patient. In the case of a preoperative prep, you may have a much longer tolerance for time, because the material is left on the skin as much as several hours before surgery.

So the situation determines what speed means, similar to spectrum of action. In general, the products are desired to be broad spectrum, but we may be talking about a situation where we're only interested in controlling the resident flora.

For example, on an atopic dermatitis

person who has a lot of staph aureus risk, we may be primarily interested in controlling the gram positives, and that may be the spectrum we're particularly interested in for antimicrobial product for that use. Again, the situation drives the specific attribute definition.

Length of action or persistence: I'll go into just a bit more detail, because that one is somewhat more complex. Finally, some of the conversations we've had lately, such as for the food area suggest that one of the attributes may be affecting us in the presence of the soils in a given situation, particularly in the food area where some of the food handling situations have very high soil and organism loads. We may want to establish that as one of the performance criteria.

Expanding on persistence for a minute: We believe that persistence means that a product exhibits a prolonged or extended activity which prevents or inhibits, number one, the growth of organisms which remain on the skin after washing.

That is, you wash your hands. You kill a

lot of the organisms. You probably don't kill them all. There are still some left. It is desirable, for example, in a surgical scrub situation for those organisms to remain very low for long periods of time. As the surgeon goes through the week, you want to keep the counts of both resident and transient quite low.

So persistence can mean keeping down what's already there after washing. It can also mean, though, preventing the reestablishment of transients that are contacted in the environment.

So there's two different perspectives on persistence here. We think there are subtle but important differences, and different products should have different persistence criteria, depending on the situation in which they're used.

If we take all these attributes then and apply them to the categories of products that are used as antiseptic wash products, we can see, for example, on a body wash category we may be talking either a limited or a broad spectrum, depending on whether we're talking about a patient pre-op body wash or a consumer body wash that deals primarily with resident

organisms.

These products typically act by persistence. That is their primary effect. They're on the skin for periods of time. They act by persistence, by one of the definitions we've talked about.

If you go down to a health care personnel hand wash situation, these are very broad spectrum, acting on primarily transient. They need to be very fast acting. However, since they are used typically anywhere from ten to 100 times per day, the interval between washing is not high.

We're primarily interested in fast acting on transients. Persistence may or may not be a necessary attribute. We don't think it is a mandatory for health care personnel hand wash.

You can see a similar thought pattern for all of these. I won't go into detail on it, but generally we're just aligning key characteristics or attributes with situational use in category product.

Just a couple of quick words on indications. This is what defines the drug product.

We believe this should be situationally defined. So we take the performance expectations for a given situation. That should drive the indications and labelling for a product.

We think that in vivo and in vitro test methodology should be the basis of substantiating that a product, in fact, meets these performance expectations for that situation.

Proposed labelling and indications, we believe, should be based upon validated, accepted standardized test methodologies. That really is a starting point for making indications and claims.

Another important point on indications: The 1994 TFM omitted indications, in fact a lot of information, on several categories of products. We believe this needs to be expanded to cover the full range of antiseptic wash products.

For example, nonprofessional health care settings, such as a consumer setting where there is still infection risk -- and we will show some of this information in a few minutes -- is not specifically addressed. In fact, antimicrobial soaps were admitted

from the monograph.

Food handling -- We have begun dialogue discussions with FDA. This is an area that needs to be defined. The use scenarios are extremely complex, ranging from eating a sandwich on a picnic to a slaughterhouse. You can imagine the range of issues that we have to deal with here. So these products very much need to situational definition and indications.

Finally, hand sanitizers, which are basically included in the monograph, because alcohol is a category one, but we still don't have clear indications for hand sanitizer and some other issues around claims and substantiation.

So you can begin to see, this is a fairly complex area. It's understandable why the time frame is lagging, but we appreciate the opportunity today to present and to discuss some of the information and data we have, and we also look forward to an interesting dialogue, as Debbie mentioned.

Finally then, I have covered the first part of our agenda. Bruce Keswick from Proctor and

Gamble will give some brief information on organism transmission that they have developed recently. Thank you.

CHAIRMAN BRASS: Thank you. Are these any questions for Dr. Dolan?

If not, as indicated, our next speaker is Dr. Bruce Keswick, who is Section Head for Clinical Research and Biometrics of Proctor and Gamble.

DR. KESWICK: Good morning. Can you hear me?

Good morning. As was said, I'm Bruce Keswick. I'm a Section Head in Clinical Research and Biometrics with the Proctor and Gamble Company.

Today I'm going to talk about risk in nonmedical, nonprofessional settings, cross-contamination, and transfer of bacteria, particularly in the home.

The points I want to make are that there are significant exposure to organisms that occur in the home; that the potential for cross-contamination is high; and that washing with plain soap is only partially effective.

In the background HCCM materials there are a number of examples of both dermal and other routes of transmission where organisms can be transferred, and the risk that the general consumer has to bacteria in their everyday life.

I want to give a few new examples that haven't been published and a couple from the literature. Handling raw meats, eggs, sponges, dish towels, other items, can transmit a high level of bacteria to the hands.

For example, uncooked whole chicken, chicken just from a grocery store, and unwrapped and handled as if you were preparing a meal can result in up to 10^7 bacteria being transferred to the hands. In that case, that's per hand.

In the experimental situation in a study that we've conducted, if you take sterile ground beef and inoculate it with e. coli and then handle it as if you were making hamburger patties or a meatloaf, you can actually transfer up to about 10^7 organisms per hand.

Wet sponges have been shown in the

literature to include even up to 10^7 organisms from just sitting on your kitchen sink. We took a wet sponge that was inoculated with bacteria and handled that. Ten minutes later, we found up to 10^5 organisms on the hands of the people who had handled those sponges.

If you look in the literature, there's a couple other good examples. Used kitchen towels that had been just in normal use for three days were handled by individuals, and then their hands were assayed. They had between 10^2 to 10^3 organisms left on their hands after touching that towel that had sat around in the kitchen.

Finally, another well known study where salmonella was inoculated into intact eggs and then those eggs were used to prepare -- used in preparations such as baking. Up to about 5 to 25 percent of the hands that were sampled from the subjects who had handled those eggs were contaminated with that salmonella. So that there was a potential for those bacteria to be passed on.

In another study to show how these levels

of contamination can actually be cross-transferred between food products in the home, we've done a new study. This is one where we are looking at the transfer of the organisms between chicken and using raw sterile hamburger as an indicator of the transfer.

Essentially, what happens in this experiment is someone handles the chicken and then handles the ground beef as if they were preparing a meal, making a meatloaf, hamburger, whatever. They do that and/or they wash their hands in between the stuff. Let's look at what happened.

The average cross-contamination of the ground beef after handling chicken but with no hand wash was about 1.8×10^4 CFUs per hand. The average cross-contamination of the ground beef when hands were washed after chicken exposure still was 3×10^3 CFUs per ml. A significant amount of bacteria remained.

So in summary, we feel that there's a significant risk of bacterial contamination and transfer that exists in nonmedical settings such as the home. Washing with plain soap is only partially effective, and there is a role for antibacterial

products in the nonmedical/nonprofessional situation.

I've given some examples of the risk that might occur in the nonprofessional setting and at home, and now Dr. Chuck Haas will present how risk modeling can be used to estimate the effectiveness of antimicrobial products.

CHAIRMAN BRASS: Can I just ask a quick question? In our interest of testing, what was the duration of hand washing with plain soap in the experiment you just described?

DR. KESWICK: I can tell you. It's right here. Hands were washed for 30 seconds, rinsed for 15 seconds, and then dried with a paper towel.

CHAIRMAN BRASS: Thank you. Are there any other questions?

DR. MAKI: What was the n on that experiment?

DR. KESWICK: I have to look. I think that was 30, but I'm not certain.

CHAIRMAN BRASS: Dr. Koda-Kimble?

DR. KODA-KIMBLE: Was the experiment done with antimicrobial hand wash?

DR. KESWICK: No, that was with plain soap.

DR. KODA-KIMBLE: Okay. You don't have any data with --

DR. KESWICK: That's right.

CHAIRMAN BRASS: Are there any other questions from the panel?

Our next speaker is Dr. Charles Haas, the Betz Chair Professor of Environmental Engineering at Drexel University.

DR. HAAS: Thank you. Good morning, ladies and gentlemen. I'm Chuck Haas from Drexel University, and I'm appearing today as an independent consultant.

I've been engaged in risk assessment work for microbiological agents for about 15 years in a variety of settings, and our use of microbiological risk assessment stems directly from the 1983 National Research Council paradigm that's been widely used for chemical risk assessment, which we applied to microbials.

The advantage of microbial risk assessment

is it permits an assessment of the consequence of an exposure in the absence of direct experiments on human subjects which might not even be doable if you're projecting for a new scenario.

Microbiological risk assessment has been used by a number of Federal agencies elsewhere outside the purview of this particular panel. My greatest experience is in water, both drinking water and surface water, where EPA has made use of the methodology in developing a number of regulations in those areas.

It's being looked at actively now in the food area by both USDA and FDA, CFSAN at FDA in particular.

The two applications I want to present to you today are an application of this methodology to a body wash scenario to model projected benefits of antimicrobial body wash products, and in a hand washing scenario to examine risk reduction by the use of the antibacterial hand washing contamination versus a control versus a plain soap.

Now in the body wash scenario, I'm

focusing on staphylococcus aureus as the organism of concern. This is a dataset on dose response done by Singh in 1971, which looked at infection as a function of initial dose of staph aureus, and responses were measured up to day six in these subjects.

The analysis of this data is somewhat complicated by the fact that staph aureus will grow and perhaps decay dynamically upon contact with skin. Our examination of the Singh data suggests that the risk appears to be both a function of dose and the time of contact, which allows growth with the skin.

Therefore, to understand the dose response relationship we also simultaneously need to understand the growth kinetics of the organism in that experiment.

So in order to do that, looking at the Singh data, we analyzed it using a growth model. The basic details of the growth modeling are that we used a logistic growth law to model microbial growth. Concomitant with that, we have antimicrobial activity on the skin, depending upon washing with previous agents. The antimicrobial activity appears to decay

exponentially with time after washing.

We calibrate the growth model by using the data, the Singh, which reported skin concentrations of staph aureus over day one to six, and in order to model dose response relationships what appears to work best with this dataset is the so called area under the curve approach, which is an approach that's used fairly widely in chemical risk assessment where you integrate some particular toxic concentration with respect to time.

So area under the curve in this context really represents time integrated microbial concentration on the skin.

So this is the dose response curve fitted to an exponential dose response relationship, which I've used in a number of contexts for bacteria, viruses and protozoa. The points represent the data points of Singh. The curve represents the best fit, and the fit is highly significantly statistically using a maximum likelihood fit test. Decay represents a dose response parameter.

So now we can use the dose response

parameter from that study along with the growth relationships to estimate the impact of various use scenarios in the context of a body wash product.

To do this, we've also made use of another dataset that was taken by Hilltop Laboratories, also on staph aureus where die-off and regrowth on skin were followed following the use of a consumer antimicrobial bar soap in one group of subjects, versus a plain or control soap on another group of subjects.

Seven washings over a three-day period were performed, and then the challenge organism, staff aureus, was administered to one group of subjects, either immediately after the last wash or 24 hours after the last wash.

From this, we could calibrate the exposure model and use that to estimate risk of infection based on the dose response curve from Singh.

This represents the fit of our model to the Hilltop Lab studies. The red lines represent both the experiment -- The red points on the red lines represent the experimental observations and fit to the

control.

So the green points and green lines represent the antimicrobial. There are two sets of lines, because one set of data and models represent the subjects who were administered the microbial challenge immediately after the last wash, and the other represents the subjects who were administered the microbial challenge 24 hours after the last wash. So there's decay in potency.

A very, very good fit of the observations to the model. From this now, we could project what consequences are of particular use scenarios, and the scenario that I looked at for the purpose of the calculation was to suppose that initial staph aureus inoculum of 100,000 organisms per square centimeter occurred just after washing with either a control soap or a germicidal soap.

The parameters from the Hilltop Lab studies were used to assess that data, as was the dose response relationship from the Singh data, and now we examine the risk of infection over a 24 hour period from that loading, assuming no intervening washing

within that 24 hour period.

Based on this -- and I would focus your attention here to the last column of the table -- we project out the risk to subjects under those two use scenarios, and based on this assessment of the body wash situation, there's about a twenty-fold difference in risk from control soap versus the antimicrobial, based on this data.

Okay. Now I would like to proceed to the second scenario, which is exposure in a hand washing situation.

After contact with some source of contamination, perhaps the chickens, as Dr. Keswick described, for example, or other sources of soil or contamination, there is an initial challenge of organisms. In the intervening time that would elapse between that source of contact with the challenge and a hand-to-mouth transfer within the same subject, there is a potential for either regrowth or decay of the organisms to occur.

Some fraction of the organisms remaining on the hand at that point then is transferred to the

mouth and represents an oral ingested dose. So simply, if you multiply those three numbers together, you get an estimate of the dose of organisms that would be transferred as a result of that single instance.

To assess the parameters pertinent to that scenario, we've used a dose response curve of Shigella, and I should just comment here parenthetically -- I know there's a lot of interest of late in enterohemorrhagic e. coli.

There is some suggest that the potency of enterohemorrhagic e. coli is similar to the potency of Shigella, although there is no human dose response data available, fortunately, to test that; but it has been used in a number of circumstances to model the potency of that organism.

So we used the dose response of Shigella, a loading of 10^6 to 10^7 CFU per gram, based on fecal material, transference of that material to hands as estimated by soil contact data. There's a rich literature in the field from the environmental field on how many milligrams of soil are transferred to

hands as a result of various contact scenarios.

Reduction on the hands is estimated based on tests that were performed on reduction by Serratia Marcescens in the one-wash version of the health care personnel hand wash test, and finally ten percent transference from hands to mouth is assumed as the last stage in the process.

Now with that, and also running the relevant uncertainties in a Monte Carlo context here, there are two curves that are developed. The red curve represents the projected results from the use of plain soap. The green curve represents the projected results from the use of the antimicrobial soap.

I've highlighted here the medians of those probability distributions, and there's about a tenfold reduction in risk at the median point, as contrasted between those two agents.

So the take-home lesson I would offer here is that improving the immediate germ reduction via the use of a germicidal hand soap in this scenario appears to provide a significant reduction in risk.

Finally, let me highlight three bullets I

would like to leave you with. First of all, I believe that the methodology of microbiological risk assessment is applicable to the exposure scenarios I've described here, or certainly related exposure scenarios.

Second, it does provide a route to benefit assessment which does not require large human trials.

Third, the application of MRA to the scenarios here indicates substantial benefit to antimicrobial product usage.

Thank you.

CHAIRMAN BRASS: Thank you. Are there any questions from the panel? Yes?

DR. GILLIAM: On your first --

CHAIRMAN BRASS: Please use the mike.

DR. GILLIAM: On the first graph where you talked about body wash, you showed that there was a 20-time reduction in the risk.

DR. HAAS: Yes.

DR. GILLIAM: Was that with the group that was inoculated immediately after hand washing or 24 hours later, or both?

DR. HAAS: No. In that scenario, I'm simply looking at inoculation immediately after body wash.

CHAIRMAN BRASS: Dr. Maki.

DR. MAKI: It's sort of an inelegant statistical tour de force, but I'd make the observation that trying to extrapolate too much from this type of a model can be very hazardous.

You're working here based on your assumptions based on laboratory adapted strains, very small numbers of individuals that you have data on the kinetics of what's happening on the skin, and trying to extrapolate to a huge range of pathogenic microorganisms that may have very different behavioral patterns, very different ecologies on different individuals that influence these kinetics on which you base these descriptive equations.

You might find a very different real world than the modeling might suggest.

DR. HAAS: No, I agree, but then let me go from there to another benefit in the methodology. Having established a model like this, you can ask a

"what if" question. What if the growth rate was ten times greater? What if, and so forth? See if those factors could, in fact, make a substantial difference.

CHAIRMAN BRASS: If there are no other questions, thank you.

Our next speaker will be Rhonda Jones, President, Scientific and Regulatory Consultants, Inc.

MS. JONES: Good morning. We are now at the final piece to the industry presentations. My name is Rhonda Jones. I'm a registered microbiologist and President of Scientific and Regulatory Consultants. I'm pleased to be here today to address you on performance expectations of topical antimicrobial wash products.

Briefly, I'd like to set the stage using an overview of background information on attributes and test methodology in order to directly address the first discussion point put forward by the FDA. This will be followed by a brief overview of many outstanding issues of the testing conditions and methodologies outlined in the 1994 TFM.

Finally, I'd like to address several

formulations in order to illustrate their effectiveness, first, as the performance criteria and methodology outlined in the 1994 document, as well as reviewing specific publications on each of these formulations detailing positive clinical outcomes.

One of the six assumptions underlying the health care continuum model is the necessity of having standardized, defined and peer reviewed methodology to encourage reliability, reproducibility and comparability of test results.

So how do we get there? What's the process? We must first achieve method standardization. Although there are several organizations which develop test methodology, historically the American Society of Testing and Materials, ASTM, has been responsible for generation and adoption of methods in the area of topical antimicrobial products.

We recommend that this practice continue rather than the agency being responsible for detailing methodology. We believe that this offers a degree of flexibility, and yet meets the needs of standard,

defined and peer reviewed methods.

Upon arriving at or returning to standard methods, validation of these methods will be necessary and may utilize some of the formulations I will discuss momentarily. This will then allow the selection of appropriate statistical methods and performance criteria which will be based on clinical outcomes.

So where are we in the process today? The TFM included modifications to methodology which are not supported by historical data nor are they part of the existing ASTM published methods. The change in test parameters are not well defined, and thus the methods may not elucidate the appropriate product attributes.

In addition, use situations may not be reflected by some of the proposed methodologies, and effectiveness criteria may not be linked to clinical data.

The following three slides are a direct response to the first discussion question put before the panel by Debbie Lumpkins this morning. The tables

simply pair the test methodology available today to evaluate the microbial effectiveness of each of the six health care continuum model categories with each of the attributes as discussed.

I have also denoted, using an asterisk, the methodologies have been proposed in the TFM. So for measurement of spectrum, we have minimum inhibitory concentration tests, time kill testing. For speed of kill, we may utilize time kill testing, AOAC chlorine equivalency tests, and various in vivo methods.

The AOAC tests -- you may not be familiar with -- is being carried over from the USDA regulation of products in the food handler area.

For in vivo effectiveness against transient flora, there are several methods at our disposal: The health care personnel hand wash; a draft method cited here as the hand rub which is based on Rotter's publications; the cup scrub methodology agar patch, a generally used hand wash test; and skin preoperative preparation.

For in vivo effectiveness against resident

flora, we have the modified Cade cup scrub, surgical scrub, and preoperative preparations.

Finally, persistent activity may be measured by the health care personnel hand wash, the general use hand wash test, modified Cade, surgical scrub, preoperative preparation, cup scrub or Rotter patch.

In the industry response to the monograph we offered a detail explanation of the various issues with each of the testing conditions and methodologies proposed by the FDA. These issues need to be resolved prior to proceeding with method validation.

Briefly, I would like to outline these issues for each method proposed in the monograph. The National Committee for Clinical Laboratory Standards' MIC test is proposed test the in vitro antimicrobial spectrum. However, that method was optimized for clinical laboratory testing and may not be appropriate for testing antimicrobial active ingredients or final formulations, due to insolubility or interferences due to the growth media.

In addition, the type, source and strain

of the test organisms remains unsettled, and lastly, we have proposed a differentiation in the extent of testing necessary for active ingredients versus their final formulations.

Next we have the time kill test, which is a method to evaluate the rate of bacteriocidal activity. Although initially no protocol was specified, we answered the FDA's request for such a method which was submitted to the ASTM and is currently under review for adoption. However, we recognized that this type of testing may not be appropriate for all formulations, especially waterless formulations and other formulations which may have insolubility issues.

Also, no performance criteria was specified, and additional questions remain regarding contact times, -- those proposed by the FDA do not simulate the use setting -- growth media, test concentration, and the appropriate test controls.

For the health care personnel hand wash, although the ASTM methodology was cited in the proposed rulemaking and is part a duplicate of this

method, several key changes were made in the 1994 proposed rule.

These changes have not been validated, and stand in deference to a large body of historical data. These changes may affect the reproducibility of the method, and have not undergone the ASTM peer review process.

Other issues with the proposed rule remain uncertain, such as baseline collection, the incorporation of immediate neutralization, the hands contamination and sampling techniques, the performance and statistical criteria.

As it is key to a later discussion, neutralization is a technique utilized in bacteriocidal tests to halt further antimicrobial activity at a desired time point. Recent research has shown that the health care personnel hand wash and a surgical scrub test methodology has historically had inadequate neutralization, thus producing exaggerated effectiveness data. I will illustrate this shortly with some data from the literature.

The ASTM surgical scrub methodology is

also detailed in the 1994 TFM. Similarly, the outstanding issues with this method are the need for immediate neutralization, inappropriate performance and statistical criteria, testing controls and sampling times.

Finally, the proposed rule cited for the ASTM standard for evaluation of skin preoperative preparations: Although the proposed rule again cited the ASTM technique, there were many areas to be delineated, including the criteria for baseline populations for the test sites, the possible need to utilize occlusion to achieve baseline for the dry site, the performance criteria, the statistical criteria, and the appropriate controls for the test.

So now to move in a different direction and to better demonstrate the need to revisit some of the test methods and test conditions as proposed by the 1994 monograph, and certainly the performance criteria, I'd like to introduce five examples of formulations which offer a unique analysis of the test methodology and performance expectations.

These models have been selected based on

the availability of laboratory data such as that required by the health care continuum model or the TFM. In addition, some of the examples cited are linked with clinical studies or publications describing positive clinical outcomes.

Some of the examples are recognized formulations within the health care industry, such as Chlorhexidine and povidone iodine. Through the use of these examples, I would like to show that formulations with demonstrated clinical outcomes fall short of the current performance criteria proposed in the TFM.

Our first example features chlorhexidine gluconate or CHG containing formulations. As these formulations are not over-the-counter drugs, they require new drug applications, which involves an extensive review of safety, efficacy and chemistry data, as well as the manufacturing processes for each individual formulation prior to its introduction to the market.

Chlorhexidine formulations are considered to be among the most effective available for health care professionals today to prepare surgical sites, to

prepare the OR team for surgery, and to reduce nosocomial infections.

There is an extensive database of in vitro and in vivo and clinical data to demonstrate the effectiveness of these formulations. Due to time constraints, we will focus only on the in vivo data available for each of these examples.

This messy table lacking the bottom line here -- who knows where these things go with these electronic presentations -- illustrate data generated on multiple four percent CHG formulations and a two percent CHG formulations in the ASTM health care personnel hand wash test.

As stated earlier by Debbie, this test measures the bacteriocidal activity and removal utilizing Serratia marcescens as a marker transient organism. The table specifies specifically where delayed neutralization is used and immediate neutralizations, so that you can see the impact on the actual log reduction values as we move through the table.

The performance criteria for the --

proposed by the TFM is listed across the top in blue, two logs of reduction at the first wash, three logs of reduction at the tenth wash, as Debbie noted.

In red, you see everywhere these particular formulations fail the performance criteria recommended by the TFM. Again, very obviously, a part of what is going on here is the need for immediate neutralization.

You can see that with delayed neutralization the log eduction values are much higher as the activity of the antimicrobial continues after sampling.

The data clearly show the decrease in the log reduction when immediate neutralization is employed. However, when effective and well respected chlorhexidine formulations are properly and immediately neutralized, they do not pass the performance criteria proposed in the 1994 TFM for use as a health care personnel hand wash.

The ASTM surgical scrub test was used to generate the data shown in this table. The surgical scrub test measures the reduction in resident flora

following a standard surgical scrub procedure.

The reductions are measured after a single scrub on day one, the second scrub on day two, and eleven scrubs later on day five. Again, the TFM performance criteria is listed in blue. One log reduction, two, and three logs of reduction at each of the different sampling points is what is proposed.

Again, that particular methodology employs delayed neutralization. As you can see from the data shown here, delayed neutralization again allows for much higher log reductions; whereas, when the formulations are immediately neutralized, you begin to see the impact of instantaneously stopping that action as you're recovering the bacteria off of the hand.

In red we see where each formulation has, in fact, failed to meet the performance criteria established by the TFM. Interesting to note, these are all the formulation tested by four different people.

Nonetheless, when chlorhexidine formulations are properly and immediately neutralized, they do not pass the performance criteria proposed in

the 1994 TFM for surgical scrub use.

So as a review of an example provided by chlorhexidine formulations performance in these two tests, we see the need for method standardization to reduce the variability in the tests and afford greater comparability among test formulations.

When effectively neutralized, approved NDA formulations do not meet the performance criteria established for the TFM for OTC drug use. Thus, these effective formulations would not be available as surgical scrubs or health care personnel hand washes under the proposed rule.

Moving along to our next example is a 7.5 percent povidone iodine scrub, which is equally well respected for its clinical effectiveness. From a regulatory standpoint, it is classified as an over-the-counter drug and as category 1 for safety and effectiveness.

Category 1 ingredients are considered safe and effective for each of the intended uses in the monograph. The literature includes extensive laboratory in vitro and in vivo data, as well as

clinical publications.

This table depicts the formulation's performance in studies following the ASTM surgical scrub test. Again, the criteria are listed in blue across the top, and we have the issue of delayed neutralization in the existing test methodology. The performance criteria is one, two and three logs of reduction at each of the different time frames.

The first two examples show the effect of delayed -- can be compared to the immediately neutralized formulation -- to show the effect of the institution of the immediate neutralization step. Again, everywhere in red is where the formulation would be shown to fail the performance criteria.

Irregardless of the povidone iodine formulation neutralization, each of these formulations would fail the proposed reduction levels for surgical scrubs.

As the data presented here is generated in multiple laboratories on the same formulation, it further illustrates the need to strive collectively toward greater standardization of test methodology and

to facilitate reproducibility and comparability of test results.

The povidone iodine example illustrates the variation, due to lack of standardization of the test methodology. However, whether neutralized or not, formulations with a category 1 ingredient such as povidone iodine do not meet the proposed criteria for OTC health care antiseptic drug products.

Our next example focuses on a one percent Triclosan formulation. Triclosan is category 3 for safety and effectiveness for health care personnel hand washes. The specific formulation we will track is newly launched in the U.S. and is substantially similar to formulations available internationally.

Extensive in vitro and in vivo microbial data and irritation studies have been compiled, as well as published studies suggesting a positive clinical outcome. As we want to stay on schedule today, there's just a brief time to whip down through each of these reprints, but some of the authors are going to be with us later to describe their studies.

The first study, published by Marshall,

describes the reduction of MRSA in a hospital upon the institution of the one percent Triclosan soap for patient bathing prior to admission and hospital -- and throughout hospitalization.

The author reports a concomitant reduction in the presence of ciprofloxin resistant strains over the one-year period. Paul Marshall, the author of the study from Sutherland Hospital in Australia, will provide additional detail on his study later today.

The Webster 1991 and 1992 reports showed the effect of institution of the one percent Triclosan formulation for staff hand washing with no other infection control practice changes for a seven-week study. The formulation replaced a four percent chlorhexidine gluconate product.

Webster reports that new MRSA cases in the neonatal intensive care unit were reduced from 3.4 percent to less than two-tenths of a percent. In addition, the staff reported less skin irritation and a higher rate of product acceptance, especially from those staff with sensitive skin.

Based on this prospective study, Webster

and co-workers, the third citation here, began a one-year trial, continuing the same infection control regimen. The authors report a gradual elimination of MRSA from the neonatal unit, as well as the special care nursery.

The authors note that, although the occurrence itself is insufficient to confirm a causal relationship, it is related temporally and was duplicated.

The final citation by Brady and co-workers reported that, following the institution of the one percent Triclosan product for whole body bathing, in addition to routine post-operative surveillance and the reduction in antibiotic use post-operatively, coincided with the significant reduction in the number of MRSA carriers and infections.

So again we move to test data generated using the ASTM health care personnel hand wash test. This study was performed at 15 and 30 seconds using 5 mls of product, and included a comparative two percent chlorhexidine formulation.

The TFM criteria is noted in blue. Two

logs of reduction is required after a single wash. Three logs of reduction are required after ten consecutive washes.

Again listed in red are each of the time points where these formulations do not meet the performance criteria proposed.

It is important to note that not only does the one percent Triclosan formulation not meet the criteria, neither does the two percent chlorhexidine formulation, although the one percent chlorhexidine formulation does move slightly above the performance level for wash one, whereas the two percent chlorhexidine remains just below.

The one percent Triclosan example demonstrates the comparable in vivo effectiveness of a Triclosan formulation to a chlorhexidine NDA formulation when CHG is properly neutralized. The reviewed studies suggest positive clinical outcomes coincident with the institution of the one percent formulation and allow correlation to laboratory data.

Lastly, neither the NDA nor the one percent Triclosan formulation in this case pass the

TFM requirement to be offered as health care personnel hand washes.

An additional Triclosan example is provided by a .3 percent formulation which is currently available for use as the health care personnel hand wash. This formulation is comparable to formulations which may be offered for consumer use.

Triclosan is classified as category 3 for effectiveness and safety as a health care personnel hand wash. Tracking this formulation also allows review of laboratory in vitro and in vivo data and a single report of clinical outcome.

In addition, the formulation has been shown to demonstrate a 92 percent and a 98 percent reduction, respectively, against hepatitis A and polio virus, as compared with lesser reductions for four percent chlorhexidine formulations.

This data was generated using a new ASTM test method which measures removal of viral contaminants from the fingertips of human volunteers. Dr. Syed Sattar of the University of Ottawa will address this type of testing in detail later in the

program.

Zafar and co-workers' published clinical study reported a single change to the .3 percent formulation for hand and body washing halted an outbreak of MRSA in a neonatal unit. The authors report that the unit was free of MRSA for over three and a half years.

Dr. Abdul Zafar from Arlington Hospital will review their findings and their continuing success for a total of eight years later today.

The .3 percent Triclosan example, as evaluated again in the health care personnel hand wash, shows where the TFM, in blue again, has required two logs of reduction in the first wash and three logs of reduction in the tenth wash, again shows that this particular formulation, using a 60-second wash time with 5 mls of product, does not meet the TFM.

The .3 percent Triclosan formulation offers a report suggesting a positive clinical outcome concomitant with the institution of the soap. An additional study demonstrates the utility of a Triclosan formulation for viral removal. However, the

formulation does not meet the TFM performance criteria to be available as a health care personnel hand wash.

Our final performance example today is a 1.5 percent triclocarban bar soap. Triclocarban or TCC is classified as a category 3 ingredient for effectiveness, and category 1 for safety, although the particular formulation I will discuss is an NDA product.

For this example, we have available in vitro and in vivo laboratory studies, as well as two recent studies demonstrating a statistically significant reduction in staph aureus associated with atopic dermatitis.

Although Dr. Jim Leyden from the University of Pennsylvania School of Medicine will be up next to discuss this study in detail, the slide contains a brief overview of the data collected during two studies of patients exhibiting atopic dermatitis.

As patients with atopic dermatitis have a high frequency of colonization of staph aureus, they provide an excellent opportunity to study the effectiveness of topical antimicrobial wash products

used daily for whole body bathing.

Both studies demonstrated a statistically significant reduction of staph aureus -- reduction values are listed here and here for the 1.5 percent TCC versus plain soap -- and an improvement in the dermatology scores, listed here -- I apologize. We've lost the lines which made it a little easier to track.

So both studies demonstrate a significant reduction in staph aureus and an improvement in the dermatology scores for use -- one use of the bar soap over a non-antimicrobial soap. These studies suggest a clinical improvement in dermatitis resulting from the use of an antimicrobial bar soap.

Again, we move to the laboratory data. This table depicts three different in vivo methodologies that we haven't really gotten into up to this point. These methodologies are used to assess antimicrobial effectiveness of the particular one percent TCC formulation.

The studies utilized plain soap or placebos as controls -- Again, we're missing a line here. These studies utilized plain soap or placebos

suggested clinical improvement against staph aureus in atopic dermatitis cases to a range of tests proposed in the health care continuum model. In addition, the data clearly show a statistically significant benefit of the formulation over plain soap and water against transient and resident flora for immediate and persistent antimicrobial activity.

So to conclude, I have reviewed five performance examples in order to illustrate the areas where continued collaboration to standardize and define methodology and in order to achieve reliable, reproducible, and comparable test results.

The ASTM Antimicrobial Committee can provide a peer reviewed consensus process to achieve method standardization. In order to work toward this goal, the SDA/CTFA Coalition has written and submitted to the ASTM many methods where standards did not previously exist.

These methods have been and are continuing to be extensively peer reviewed by microbiologists expert in the field. The ASTM provides a forum by which these methods can be maintained and published.

We recommend that the FDA continue their practice of citing this methodology rather than detailing the methodology in future rulemaking.

Finally, once achieved -- once standard methodology is achieved, it can be used to validate the methods. This will allow the meaningful selection of appropriate statistical and performance criteria by which to measure each attribute, while linking the laboratory effectiveness to positive clinical outcome reports.

So to take a deep breath and step back and offer a few concluding remarks overall to the industry presentations: The health are continuum model provides a useful frame of reference for evaluating these products.

Health benefits are associated with a full range of antimicrobial wash products. Situational factors, i.e., intended use, should direct performance expectations and testing requirements.

We have significant concerns with the test methodology and the performance criteria presented in the 1994 TFM. Additional work is needed before the

rule is finalized. Standardized test methodology is the logical next step.

Thank you.

CHAIRMAN BRASS: Thank you. Questions from the panel? Dr. D'Agostino.

DR. D'AGOSTINO: I'm not sure I'm getting the message completely. Are you saying that the TFM criteria are too stringent or that there's so much variability in the method that the labs can't meet it individually, but some sort of average might make it? I'm missing --

MS. JONES: Well, I believe, actually, it is a combination of both, and perhaps future performance criteria would be XYZ reduction plus or minus the standard deviation of the methodology, which would come out of any validation work that was done.

DR. D'AGOSTINO: In some of the presentation or pieces of the presentation you made here where you just an individual lab, was that just one testing within that lab as opposed to some sort of averaging of numbers?

MS. JONES: Yes. The publications --

typically, yes. That was one study. It may have included anywhere from six to 30 human subjects, and that may have been duplicated if there were other formulations. Typically, in the publications I selected the particular formulation, but there may have been three or four other comparative formulations also being run.

DR. D'AGOSTINO: It's very hard for me to sort of pull a message away when there's just an average pulled out there, and I don't have a sense of variability; but I think, just to say again, you think the criteria is too stringent, even if the variability were being taken care of?

MS. JONES: I believe so. I think the povidone iodine example probably illustrates that better than anything, because in all cases it was well below the performance criteria.

CHAIRMAN BRASS: Dr. Tong?

DR. TONG: In the last example of the TCC 1.5 percent, was the TFM standards or tests applied in that situation, because you indicated that clinical benefit in the health care continuum model standards

showed benefit, but you didn't mention anything about the other.

MS. JONES: I showed a health care personnel hand wash on a single wash that showed a reduction, I believe, of 2.8 logs. So that would be above the 2.0 TFM requirement. In the case of the Cade test, as well as the cup scrub test shown in that table, those were not proposed in the TFM. They have been proposed by the industry in their health care continuum model to support both the general antimicrobial hand wash and body wash categories.

DR. TONG: I have one other question. Could you -- Thank you. Could you comment on an earlier statement, that you indicated the industry wanted only the active ingredients to be addressed when it comes to spectrum of organisms affected and not the final formulation. Can you --

MS. JONES: No, no. Yes, I would definitely like to clarify that point.

What we suggested was actually just an alteration in volume of testing between the two. The TFM currently recommends testing on 1300 strains for

both active ingredients, the formulation, the final formulation and the vehicle.

We believe that was somewhat onerous and that the active ingredient could be tested on a large number of strains. We suggested the strains listed -- a slight modification of the strains listed in the TFM plus four clinical isolates of each, rather than 25.

That would be for the active ingredient, and then a subset of those strains was proposed for testing of final formulation, and that subset of strains was matched to the use setting. So in the case of food handlers, it would be test strains that were specific to organisms that would be of concern in food preparation or processing. It's matched to use setting.

DR. TONG: Thank you.

CHAIRMAN BRASS: Dr. Koda-Kimble.

DR. KODA-KIMBLE: One of the issues for the over-the-counter panel is safety, and you briefly mentioned that one product was less -- it had less irritant qualities. I have two questions.

One is: Does the industry have any

suggestions as it relates to tests for irritation? The other issue that was brought up by the 1974 panel, was it, was a concern for overgrowth of gram negative organisms in skin wash or body wash products. Are there any concerns about that from the industry, and are there any tests you might suggest to evaluate that?

MS. JONES: Okay. I love multi-part questions.

Going back to your first original question, the group that's been assembled are microbiologists. So they are expert in this area of antimicrobials. Oh, somebody else wants to take it. Okay, great.

CHAIRMAN BRASS: Please identify yourself when you go to the mike.

DR. DOLAN: This is Mike Dolan, Gojo.

You'll notice on the attribute list, we did not include irritation as a primary attribute. The reason for this is we believe, based on extensive experience, that the marketplace will sort out the issue of skin irritation.

For example, I think there are a couple of dermatologists in some test labs in the room that spend a substantial part of their time demonstrating the irritation potential of these products. We have cases in our company, for example, where product switches have been very pronounced, because we've developed low irritation versions.

I think everybody in the industry today is working on the balance between antimicrobial kill efficacy and skin irritation. We don't think skin irritation ought to be specified in a monograph. The marketplace itself and the development of the products will take care of that.

There's routine screening of these products by skin patching testing, sensitization testing, use panels, wash tests. If there are primary irritation problems, they show up in the development and use of the products, and they disappear fairly rapidly.

So we don't think that irritation needs to be a primary specified attribute.

CHAIRMAN BRASS: Ms. Jones, if you could

return to a microphone to answer this. Thank you.

MS. JONES: I believe, in the 1994 TFM, they felt that that particular issue had been answered by subsequent studies. Debbie is nodding her head.

CHAIRMAN BRASS: If I could ask a couple of questions.

MS. JONES: Sure.

CHAIRMAN BRASS: My first question is: There seem to be the greatest discordance between the TFM standards and the data you presented on the day five multiple wash, higher level kill requirement. is that observation accurate, and what do you feel is the relevance, particularly for a product like a surgical scrub, of a day five/eleven scrub standard?

MS. JONES: The surgical scrub test, I think, was developed quite a while ago to try and mimic, at least in the eighties, what they call a standard frequency for that type of formulation. Certainly, we would expect that the fifth one might offer higher variation, and those things would be sorted out of the validation methods -- validation of the methods. So --

CHAIRMAN BRASS: I'm sorry. Do you think it is appropriate to maintain as a standard a higher log kill on a day five for a product that already is effective on day one?

MS. JONES: I see your question. I think -- Do you want to take it, please, Dr. Leyden?

DR. LEYDEN: Yes, it's a good question, I think. Jim Leyden, University of Pennsylvania.

That original test when it was first developed in the ancient days when some of us struggled with this was proposed by people from the Sterling Research Institute, and one of the attributes that was suggested that could be useful was persistence, and it mostly revolved around hexachlorophene; and with chronic use with that particular molecule in a detergent based system you could show that over time that the effect was greater.

Well, it just so happened, that was the time points they picked. It wasn't that they picked those time points thinking, well, that would be a good time point to measure something if someone is going to open my heart or your brain, where you're really

interested in how much can you reduce bacteria on that hand and how long will that last in terms of an operation, because presumably, if you're going to operate on you and then me, you're going to do something in between, hopefully. Yes, right, especially if I'm second, you see.

CHAIRMAN BRASS: Thank you. I just would like to reinforce the point Dr. D'Agostino made. In terms of evaluating the data you presented, the absence of presentation of variance and the numbers involved in each of those studies makes it very difficult to assess whether the discordance from the proposed standard is due to the inadequacy of the standard or the inadequacy of the test attempting to meet the standard.

In our trying to resolve that, I think those kinds of details are very, very important.

MS. JONES: Right. Certainly, we will provide you with the full publications that support those methodologies, so that you can look at those.

CHAIRMAN BRASS: Or even if you just --

MS. JONES: I mean, I think they've

already been submitted, but not in that frame.

CHAIRMAN BRASS: In the summary -- Again, in trying to summarize the data, those test characteristics -- I mean those study characteristics would be very important in tabulating that kind of summary table.

MS. JONES: We think it's important to start by standardizing the method and then performing the validation study where you can incorporate that into the performance criteria, again XYZ log reduction plus or minus whatever the standard deviation for each of the different tests is.

CHAIRMAN BRASS: Thank you very much.

MS. JONES: Thank you.

CHAIRMAN BRASS: Our next speaker will be Dr. Jim Leyden from the Department of Dermatology, University of Pennsylvania, speaking on antimicrobial use in the nonmedical setting.

DR. LEYDEN: Thank you. Elaine Larson pointed out to me that the CV that you all have looks like I died ten years ago. So I would just tell you that, as a dermatologist, my area of -- one of my

primary areas of research interest has been trying to understand what constitutes the reasons why certain groups of bacteria are found on different areas of the skin, how infections occur, the role of microorganisms in skin disease, and I spend a substantial amount of time trying to develop ways of measuring in vivo antimicrobial activities of antibiotics and non-antibiotics.

So I was asked if I would first present an overview of why these kinds of things may have utility in the nonmedical setting. I think there's a substantial group of individuals out there that I'll very briefly detail for you that can benefit from such products, and then say a few things about some of the methodologies other than what have been presented here, which could be considered in trying to develop ways of understanding how effective these products are.

I think there are enormous amounts of data available on different methodologies, all of which can provide very, very meaningful insights when well designed studies that ask specific questions are used,

attention to detail like neutralization which is a major problem if it's not paid attention to, but can then be correlated, as you just heard, with clinical experiences and come up with reasonable guidelines to understand which formulas work, which ones don't, which ones work better than others.

Anyway, these materials are often called body washes. I think it's important to recognize -- or soaps. They really aren't soaps. Most of them are detergent systems. There are increasing uses of other delivery systems, lotions, foams and other things that have less irritation potential, particularly for those individuals who need to wash on a frequent basis.

Here are some of the more obvious, at least to me, areas where populations exist. I'll start here with the hands.

You've heard a little bit earlier from Bruce Keswick and, I think, the agency has recognized that there are plenty of examples of individuals having their hands contaminated by potential pathogens. I'll just very briefly show you that the integrity of the outer layer of the skin, the stratum

corneum, is very important as a defense mechanism.

There are large numbers of individuals in this room, including myself, who have compromised stratum corneum. That makes us more vulnerable to colonization and subsequent invasion by potential pathogens, and there's a large group of individuals who carry very high numbers of staph aureus on their skin with varying degrees of immune competency and, depending on the virulence of the strain, it can be harmful potentially to that individual or to others in their environment.

This is the hand -- Elaine, this is Kermit -- you remember Kermit, the animal caretaker in our department -- after carefully washing his hands on his way out the door on the way home. You can see, there's an interesting mixture of gram negative, gram positive and others on his hand.

A patient in our clinic with chronic eczema with normal appearing hands who's got staph aureus and a variety of other organisms, and my son, the lawyer, after changing the diaper of his perfect son known now in Philadelphia as "the Dauphin," since

he is attended by a variety of individuals on a 24 hour basis.

Just parenthetically, his wife, my daughter-in-law, two weeks ago had a conjunctivitis which I cultured and grew out e. coli and staph aureus. I think the e. coli probably got there via this mechanism.

So that's one group I've very sketchily talked that others have talked about. Let me just show you the stratum corneum. In dry skin there are microscopic fissures which, when present, lead to uplifted scales that we can then see, and we call dry. This provides a portal of entry for microorganisms.

Many years ago we showed that Group A streptococci inoculated on totally normal skin would rapidly die, mostly because of inhibition by skin lipids, but with microscopic subclinical scarifications the same organisms would very quickly invade and begin the process of infection.

We've shown, years ago when we were studying various agents in terms of their effect on wound healing, in a large number of individuals that

we did a variety of things with a variety of dressings that after a day or two, somewhere in the neighborhood of 30 to 40 percent of these wounds -- and this was in students at Drexel and University of Pennsylvania desperate for cash who participated in these experiments -- that about 30 to 40 percent of them became heavily colonized by strains of staph aureus which, in some cases, were virulent enough to cause a purulent -- a host reaction, but in other circumstances were at least able to inhibit and delay the process of wound healing.

So that's a very common potential area where people using effective antimicrobial agents on a daily basis could have residual activity, material with activity that could minimize that first all-important step of colonization before infection can take place.

I'd like to spend a little time on atopic dermatitis, which here you can see is obviously secondarily infected, and there are primary lesions elsewhere peripheral to the lesion.

Many years ago I showed that, even in

clinically noninfected situations such as this typical inflamed area of atopic dermatitis, this agent non-colored slide shows you that there are hundreds of thousands to millions of staph aureus lesions in the lesions, and in skin about five centimeters away there were hundreds to thousands to tens of thousands of staph aureus, and many others have reproduced these findings.

Even in clinically noninfected eczema, if one uses something that reduces staph aureus counts, there is at least an improvement clinically, and I think that's a fairly well established principle in dermatology.

More recently, we have looked at another group of individuals with less exuberant forms of atopic dermatitis, and this paper in press in the Journal of Pediatric Dermatology, looking at these very minor dry, scaly forms of eczema. About 40 percent of those lesions are colonized, whereas individuals in the dermatology clinic with non-eczema conditions, warts, etcetera -- there is also a significant colonization of lesions, about 20 percent,

uninvolved skin again heavily colonized,. and about 30 percent of these individuals have significant colonization of their hands as well as a reservoir site such as the anterior nares.

Here, I'll give you an idea of the density of these, 10^4, in these really non-inflamed forms of eczema, less than what one sees in the more exuberant but, nonetheless, a significant number of organisms which have varying degrees of virulent capacity. Many of these strains appear to be, fortunately, nonvirulent or at least the virulence cannot be easily demonstrated, but other individuals get colonized by, clearly, more virulent strains.

There's an interesting relationship between the lesion and the hand being positive. If the lesion is positive, almost for sure the hand will be positive, as will the anterior nares.

There's a rather substantial literature in HIV+ individuals indicating that there is significant colonization of the skin of these individuals, even when the skin doesn't look infected, and those of us who see patients know that dry, scaly eruptions over

most of the body are not uncommon in these individuals, and this is teeming with staph aureus.

If you have the right strain present, you can get some fairly nasty at least localized infections.

We have a paper in press, interestingly, in -- This came out of the Desert Storm operation where staph aureus infections were a problem, as they have been in all -- and streptococcal infections, as they've been in all military operations over the years.

We looked at recruits at Ft. Dix in New Jersey. After they had been there a while, living in close quarters and doing things soldiers do, I guess, staph aureus colonization clearly is different in these individuals than it is in the rest of us. This is another area, another group, who would, I think, clearly benefit from using something that was effective.

Now you've heard some of the papers in the literature. There's an ancient literature back, you know, in the late sixties and seventies, that either

showed or didn't show efficacy of detergent based antimicrobial substances, depending on the population, the rate of infection in the population, the number of subjects, all the usual things; but there were some that clearly showed that.

You heard some of the more recent studies with methicillin resistant staph aureus being eradicated by some of these detergent based materials, and you heard briefly about this study in atopic dermatitis, which was, I think, a very laborious, difficult study to do in 50 individuals who were treated either with 1.5 percent TCC or the soap without -- the detergent system without the antimicrobial.

These individuals also used a very low strength topical steroid once a day and, as you heard, clinical and microbiologic evaluations were done at different time points. In those treated with the soap with the antimicrobial, there was a difference in terms of clinical improvement in both the primary, secondary signs of dermatitis as well as the global overall improvement similar to the kinds of things

that we and others had shown in the past with antibiotics, either topically or systemically, and that this improvement correlated with a significant difference in terms of reduction of staph aureus, which is aggravating the dermatitis.

So I don't think there's any question, at least in my mind, that there are lots and lots of people out there in nonmedical environments who have their hands contaminated and have their skins contaminated by organisms that can be harmful to themselves and/or to others in their environment.

So how do you test all these things without going out and doing huge field trials? Well, I think one of the things you can do is try to identify those populations who are most obviously in need.

You heard of now two brief overviews of at least one study in one population teeming with staph aureus. There are others, as I've very briefly shown you. Then there are a variety of antimicrobial tests.

I would echo what was just said before me about the proposed criteria. When it was first showed

to me, I read it, and my comment was there's nothing that's currently used that will pass this test -- nothing -- which means either we're all fooled, which I don't think, or that tests need to be rethought.

Here's an atopic dermatitis patient. There are people out there with atopic dermatitis who have persistent staph aureus on most of their hand, and it isn't rapidly dying off.

One of the difficulties with inoculating the e. coli or Serratia is those organisms, for most individuals, when they're dumped on the hand, they start dying right away, and you have to keep reapplying it, and you have to move quickly to do these studies in order to be able to show an effect of an agent or an antimicrobial agent; but there are individuals whose hands -- bartenders, for example. They carry a lot more gram negatives.

Elaine, you showed years ago nurses carry a lot more gram negatives on their hands, even though they're washing, you know, 20-30 times a day. We also showed that, depending on what unit you're in -- If you're in the oncology unit, you've got a lot more

gram negatives and enteric organisms.

You're taking care of dermatology patients who used to be allowed in hospitals -- they're no longer allowed; they are now told to die at home quietly -- that those nurses had staph aureus on their hands.

So what you have on your hands can reflect who you're taking care of, and some modifications of the proposed tests seem in order to me also.

There are other ways of doing it, too. This is a real old slide of just wrapping up the forearm with Saran wrap. You get rapid increase of what's already there, up to millions to tens of millions. As long as you keep that hydration present, those organisms will stay there, and you have two arms, and you can do all kinds of experiments in terms of effective material.

Whether you use Saran wrap or something like a Hilltop chamber, you can expand this low density flora to hundreds of thousands to millions. You can also take axillary and perineal flora, which are much more varied and interesting and contain all

kinds of different organisms.

You can take those organisms, put them on the forearm, and wrap it up with Saran wrap or a Hilltop chamber, and recreate the armpit or the groin or the toe web space on the forearm, and then you have -- you know, you have three eczilla, six toe-web spaces or whatever you want.

Then you can do maneuvers. You could pretreat the skin for a period of time and then see how these transfer. Inocula expand or do not expand under occlusive dressings, or you can expand it and then ask can the material reduce it, and how quickly can it reduce, and does it persist over time.

So it gives you the ability to do, within the same subject, controls, untreated, vehicle treated, etcetera. It gives you a flexibility of doing within an individual a lot of work that makes it statistically much easier to show whether an effect did or did not take place.

You can use these chambers here demonstrating how much moisture accumulates under them. You can inoculate organisms. You heard briefly

about staph aureus and other organisms. Gram negatives can be inoculated. They will survive.

Again, you can pretreat for a period of time, put the inoculate down. Does it survive? Does it proliferate? Or you can put the organism down, give it a running head start, and then come along and ask, can you get rid of it? Can you kill it, and how quickly can you kill it?

A lot of tests have used variations of the so called glove juice test, putting your hand in a sterile bag with a detergent solution to remove bacteria, particularly, as we were just discussing, developed many years ago for looking at immediate as well as persistent effects.

One of the things that we have emphasized is that, if you look in the literature starting back in the thirties with Price, who did it first, that when you use that kind of technique, no matter how many times you look, you keep getting lots and lots of bacteria. You keep getting millions of bacteria, which then led to theories that there were hidden foci of bacteria under the stratum corneum of the palm.

We showed that, if you obliterate the nail space, the subungual space, and now do it that you get, with some variation, but eventually you get to the point where you have very little in the way of bacteria, and that the subungual space is an area that has an awful lot of bacteria in it.

Now that's real important. If the surgeon is going to operate on any of us and they have -- he or she has a glove on, you don't care whether bacteria that get in your body came from the fingernail -- under the fingernail or whether it came from the hand surface; but if you're talking about people in homes or other situations where the hand surface is contaminated, using a technique which samples the hand surface as well as the subungual space, when one is talking about noncontaminants like e. coli or Serratia, but one is talking about other organisms that are chronically there, that may not be the best way of doing it because of this problem with the subungual space.

We developed the technique of using this handprint which can then be digitized, and with image

analysis you can quantify these colony forming units. Then if you look at that result versus what one gets in the glove juice test with the nail spaces obliterated, you get a very good correlation.

So one can then ask -- can do the experiment easier in terms of measuring the effect on surface flora.

I'll just conclude by showing you some pictures of what a detergent does. A detergent will remove bacteria, which then very quickly -- the survivors regenerate. If you have an antimicrobial substance in it, you'll do better, but some things do even better only.

Only those of you up close can see that there are some left here. Presumably, you would like to use this material, and just showing you some data on topical alcohol solutions.

So I would just conclude by saying there are a lot of people in nonmedical settings who have on their skin, as well as at times on their hands, a variety of organisms potentially harmful to themselves and others.

There are lots of methods out there, some of which you've heard very briefly today, that can be adapted with proper attention to things like neutralization, and correlated with results such as this recent study in atopic dermatitis with some of these studies with methicillin resistant staph aureus, etcetera, that you've heard, that can then give you benchmarks.

Although it does this in the clinics, and it does this in these easier-to-do in terms of logistics and expense studies, there's a group correlation. Then these ought to be the standards.

Depending on what -- the criteria is whether it's persistence, immediate, quick kill, how long it lasts, etcetera, can easily be worked out; but the present recommendations will not do it.

Thank you.

CHAIRMAN BRASS: Thank you. Questions from the panel? Dr. Maki?

DR. MAKI: In your trial with dermatitis and the role of anti-infective agent, did the control group have the identical formulation applied,

including the corticosteroid?

DR. LEYDEN: They had everything the same except no TCC.

DR. MAKI: No antiseptic, right.

DR. LEYDEN: Exactly.

DR. MAKI: Good.

CHAIRMAN BRASS: Dr. Tong.

DR. TONG: Dr. Leyden, in your experience, can you tell us some examples of health risk from excessive use of topical antiseptic agents like we're talking about here today?

DR. LEYDEN: Yes. I can say that easy. I don't think there are any real risks at all. The detergents' systems have gotten better and better. I mean, there's been a revolution in detergent systems over the last 15 years, and there are more and more skin friendly detergent systems.

Now there are individuals who, by the nature of their skin, are more vulnerable, and there are individuals who, because of their job, are washing. As Elaine pointed out, years ago -- I mean, there are people washing 50 times every eight hours,

and one of the projects she did with us years ago was to show, if you do that with water, nothing, just water, that that's damaging to skin.

I mean, skin is well designed to resist irritation, but you can overwhelm anybody's skin if you work hard enough at it with just water. So the detergent systems have gotten better and better.

The antimicrobial -- I hear people say, well, you're exposed to all these chemicals, you know, these antimicrobial chemicals. Well, they're washed off, you know, and they really are not inherently injury producing substances.

The question of the overgrowth of other organisms which has periodically been raised -- I think it's been clearly settled that, in terms of the kinds of materials that are being used by people, that is just not an issue.

DR. TONG: Thank you.

DR. McKINLEY-GRANT: I had actually two questions. What about the issue of resistance of bacteria, particularly staph aureus? Is there any evidence that --

DR. LEYDEN: Well, the question of resistance to these antimicrobial substances actually was the subject of a discussion a year ago or so, I think, here. To make a long day short, the conclusion, I think, of everybody involved was that resistance to these antimicrobial substances is not an issue now, but obviously should be continued to be monitored, and is far less likely to occur than the way it does to antibiotics because of the nature of how these agents work.

So that's been fairly thoroughly addressed, I think.

DR. McKINLEY-GRANT: The other question -- Well, actually two. One, which was the material that was used to eradicate bacteria, that the hands were clear?

DR. LEYDEN: Oh, that last one?

DR. McKINLEY-GRANT: The last slide.

DR. LEYDEN: Yes. That's a product I will be introducing.

DR. McKINLEY-GRANT: Oh, okay.

DR. LEYDEN: No, no. That was a form of

chlorhexidine.

DR. McKINLEY-GRANT: Okay. And the other question: The public, I think, is under the impression that a lot of the antimicrobials really work for viruses. I mean, they're using --

DR. LEYDEN: Many of them do.

DR. McKINLEY-GRANT: Many of them do?

DR. LEYDEN: Yes.

DR. McKINLEY-GRANT: Okay.

DR. LEYDEN: Many of them actually do.

DR. McKINLEY-GRANT: Well, I guess we have to address that, too, at some point. I mean whether--

CHAIRMAN BRASS: Well, that goes under the spectrum of activity issue.

DR. McKINLEY-GRANT: Yes.

DR. LEYDEN; Then eventually, what do you do to allow a claim? But many of them do -- actually do that. In fact, yesterday I was looking at some people in a clinical trial, and this one patient was -- You know, I couldn't get close enough to her to look at what I was trying to look at.

She says, I have the flu. I said, well,

I got to look at you, and my nurse reached in her bag, pulled out an antimicrobial lotion and said, put this on your hands, I don't want you getting sick.

CHAIRMAN BRASS: If I could follow up a little bit on the last point you made -- I don't think there's any question that the panel believes in the germ theory of disease. I think that's not the issue.

I think the issue --

DR. LEYDEN: There are a lot of doctors who have embraced that theory.

CHAIRMAN BRASS: Rather, how to interpret the surrogate of bacterial counts in the context of a clinical efficacy. The paradigm you closed with suggests that, in fact, what we need are some classical clinical trials to anchor the surrogates before we can interpret the surrogates.

DR. LEYDEN: I think those trials -- those clinical experiences -- I don't know, you know --

CHAIRMAN BRASS: Well, clinical experience or clinical trial.

DR. LEYDEN: Classical emphasized, underlined, whatever that means -- I think there are,

and maybe some would disagree we need more, but I think there are clinical experiences with a variety of antimicrobial substances in a variety of vehicles that have been shown to have clinical benefit.

Now the most difficult thing you could do that I could imagine is to show that a detergent based material would benefit atopic dermatitis, because detergents, as we know, irritate atopic dermatitis patients more easily than the rest.

That's been done now. That's been achieved. So you can say, well, that material at that concentration has this benefit. You heard about Triclosan and MSR, methicillin resistant staph aureus, I mean, etcetera, at a concentration.

So those things -- If we agree that those experiences are well done clinical studies, then that means they have benefit. So now we go into the models, if you will.

As I say, there are many, many models that lots of us have -- will argue passionately that this model is done a little better than that model, but there are lots of good models out there, and you can

look with proper attention to details like neutralization, which has not been done -- you can look at the results in those models, and then, I think, make the correlations that, if this material works clinically and it does this in this model and it does this in this model, that maybe those are standards, that we should ask other things to at least reach that level before we feel comfortable that they will be useful in these situations -- is what I would say.

So I think there's a lot out there. I think you can only -- You know, you can always do more. I think the one thing -- there have been several discussions like this, and last year we had a two-day session. It was ironic that 30 percent of the people got food poisoning the night in between the two days, which was kind of neat that that should happen while we're discussing that issue.

Now you're getting down to like, well, what are we going to ask things to do. I think there may be a need to get people together who do these tests with people who are trying to decide which of

them is best, along with other people who have experience in developing methods in general and making clinical efficacy judgments, and then come up with a blueprint of what you're going to do; because as I see it -- and I appreciate the difficulties that people in the FDA have when they came out with that.

They had to come out with something, and the best attempt, based on the input they had at that time, was a series of tests that nothing can pass. So I mean, obviously, something has to be done, or else we have to get rid of everything and just say there will be no antimicrobial substances, which means if you get operated on, good luck.

CHAIRMAN BRASS: Well, at some level that does become a question, because, one, if there are not sufficient data, that becomes the conclusion versus whether, as you've indicated, there are sufficient data to establish surrogacy or relative value of surrogacies of a 98 percent reduction on a palm versus 2 logs in a glove kind of testing.

DR. LEYDEN: Yes. Well, I think, as far as I'm concerned, I would have no trouble. You know,

if you put me in charge of this process, I'll take care of it. I have no problem.

Now I have to convince you who have not been involved in this to make you feel comfortable. You know, I appreciate that, too. So -- but I think there is enough information out there.

There have been lots of us in this room who have been involved in this now for over 25 years. The process was started in 1972. It was supposed to be a two-year process, and here we are, still talking about it, and we're still having some of the same conversations.

Meanwhile, more and more information has accumulated that, I think, makes at least those of us who have been involved in it from the beginning feel more and more comfortable that these things can be answered. But then there keeps being new players in terms of starting from scratch almost and trying to interpret what is reasonable.

CHAIRMAN BRASS: Other comments or questions?

Because of the time, unless Dr. Larson

objects, I'd like to take a ten-minute break now, and then continue after the break with Dr. Larson. Ten minutes.

(Whereupon, the foregoing matter went off the record at 10:27 a.m. and went back on the record at 10:38 a.m.)

CHAIRMAN BRASS: Thank you very much. Our next speaker will be Dr. Elaine Larson, Dean of the Georgetown University School of Nursing, speaking to us on health care personnel use hand wash.

DR. LARSON: Ms. Lumpkins asked me to address the area of the health care personnel hand wash. She used that as an example this morning. So I'm not going to go over the usual ideal characteristics or definition of a hand wash, but I did want to really sort of run through some data as some examples of some of the unresolved issues that, I think, are still there.

Clearly, the issues have to do with efficacy testing, which we have talked about this morning, and I'm not going to talk about the specifics of the TFM, but I will end by talking about several

general areas that I think are still of concern.

I want to talk a little bit about residual activity and whether it's really needed in a health care personnel hand wash, skin health and aesthetics, the idea of irritancy and what that means clinically, and give you some data, some of our recent data on the relationship between hand washing and irritant contact dermatitis in health care professionals, and then maybe a little bit about cost/benefit ratio.

I would like to make a comment about the question about randomized clinical trials and so forth. That would be lovely. We've actually tried a couple of times to start and done blinding and randomization and everything, and in every case we have been cursed with a variety of outbreaks and other things that go on in the clinical setting that have made it pretty much impossible to do.

I think there are a few people who might be able to pull it off, maybe Dr. Maki, but other than that, I don't know if we can do it.

This is just -- I went around the hospital one day and just picked up all the health care

personnel hand wash products that were available in one hospital to show that we have a variety of things available, even in a single hospital.

Clearly -- Now this is from a housewife, and this is hand washing, pre- and post-hand washing -- do we have a pointer here? Obviously, the left is pre-hand washing, and post-hand washing with a plain soap. So there is, clearly, a reduction in transients with a plain soap.

Again, this is the same slide that Dr. Leyden showed from his group. I think he showed this slide. Clearly, efficacy -- and there is variation in products based on whether one is using a detergent base or a povidone iodine or chlorhexidine gluconate. These are just three different series of tests with ten subjects and a wash for three minutes.

Other ways that we've looked at efficacy over the years: This is a study that we did with a sample of 12 in each group randomly assigned to one of four products, a 70 percent ethyl alcohol, .5 percent chlorhexidine combination, povidone iodine CHG, Triclosan and always a control soap.

This was a health care personnel hand wash protocol in terms of the -- It was a short hand wash, but we were looking at effect on resident flora. This is not the Serratia marcescens current health care personnel protocol.

These are the baseline results in log counts for each of the products, and you can see -- now this is with immediate neutralization, and I would agree with the points that were made this morning, that perhaps some of these products are unlikely to meet the current standard in the monograph. This is after day one of 15 hand washes per day, and this is after day five. Again, this is reductions in colonizing flora.

Bottom line is that the alcohols performed the best. Povidone iodine was not very exciting at all. Chlorhexidine gluconate, even after five washes -- I mean, after 15 washes on the first day, was not very impressive. It was better after day five.

The Triclosan was not much different than the plain soap. Again, this is on colonizing flora, however. This is not a health care personnel hand

wash protocol.

This is just bacterial regrowth in this same study four hours after scrubbing with a glove on. The point I want to make here is that, although the regrowth for the alcohol, which does not have a persistent or residual effect, was a little under half a log after four hours. It still hadn't reached baseline.

So I'm not really clear, if you have a very good agent, why you need the residual, because in fact, even after four hours without the persistent effect, the alcohol -- the counts on the alcohol treated hands were still lower after four hours than the counts with the other products.

We concluded that the bacterial counts following the alcohol scrub were significantly lower than the other products, and the significant reductions in counts were sustained even after four hours of gloving, and that's without any persistent effect.

Another point I wanted to make, moving on from efficacy, then from residual effect, to the

differences in host characteristics and effect of products on skin. For example, these are some studies that we did with Jim Leyden's group in the 1980s, looking at differences in skin flora on the hands of physicians and nurses and other direct care providers on two different units. One was a bone marrow transplant unit, an oncology unit. The other was a dermatology outpatient unit.

The asterisks show the significant differences in skin flora. This is colonizing flora after hand washing, and our definition of colonizing flora required that they have the same isolate -- or the same organisms on their hands over a period of many months and a series of samples. It wasn't just a single culture. It was cultures over a 12-month period of time.

What we found is that, as you might expect, the dermatology personnel were reflecting some of the flora of the patients that they contact, as were the oncology personnel, 14 percent of whom had JK coryneforms -- that is, a multiply resistant diphtheroid -- on their skin.

This is part of their colonizing flora. As you can see, three-fourths of the oncology staff were colonized with yeast, as compared with about one-fourth of the dermatology staff.

Further, just to show you a little bit more of this, this column here, the blue, is the same oncology staff. The second is the dermatology staff. The red line are patients who had been in the hospital for 30 days or more -- in those days they did that; this was in the late eighties -- and then the turquoise, last line, is a group of -- I believe in this case it was a sample of 25 controls, i.e., people who did not work in a hospital, who were not taking antibiotics and had not had any for at least the past month, secretaries, construction workers, etcetera.

This is the percent resistance of their staphylococcal flora, both their coagulase negative and positive flora, on -- in the case of the controls and the staff, it was their hands. In the case of the patients, it was actually on several body sites, including the hands.

The point of this -- and this is just some

of the antibiotics that we tested these strains against. The point is that, for every antibiotic against which we tested, the oncology staff colonizing flora was significantly more resistant to every antibiotic we tested than of the dermatology staff or the patients, again, I think, reflecting -- and this was significantly correlated with frequency and intensity of touching of patients.

We know that this isn't from handling antibiotics, because pharmacy personnel do not have antibiotic resistant flora, but nurses and physicians in direct contact with patients do.

The whole point of this is that there is a constant exchange, clearly, between the patients and the hands of the health care personnel, and we have clear evidence now, not just from our work but from other people's work, including Dr. Maki's, that the hands of health care personnel can be reservoirs of antibiotic resistance.

Now what does this have to do with our conversation today? What it has to do with is that I think there are differences in the need for antiseptic

products perhaps, depending on the level of risk or the kinds of exposures that people have.

The other thing that is different is that we have a number of host characteristics that may have an influence on a choice of an antiseptic. This is actually from a long time ago. This is my doctoral work in the 1970s, but the risk for colonization -- again, colonization means on clean hands in a series of cultures, not once but over a period of months. So these are colonizing flora, not transient or contaminating flora.

What is the risk of being colonized with gram negative bacteria, and comparing hospital personnel and, again, a group of controls. In this case, the sample size was well over 1,000 individuals studied for over a year.

Men have a 4.5 times greater relative risk of being colonized for long periods of time with gram negative bacteria than women. Those who report washing their hands greater than eight times per working shift or eight times in an eight-hour period have a three times -- Those who report washing their

hands less than eight times per shift have a three times greater relative risk of being colonized with gram negative bacteria, and individuals over 55 have a three and a half times greater risk of being colonized with gram negative bacteria as well.

Again, my point is that some of our titling of health care hand wash may be a misnomer, that there are lots of other things going on, and food handling, daycare providers, other folks may be in a similar risk category for some of these things as health care personnel.

I just wanted to end by talking a little bit, showing you some recent data from some studies that we've conducted on the effects of hand washing on the skin.

Let's see now. Oh, this is just a study that we did, because there are new products out there, these protectant lotions that have a dimethycone or some kind of a mechanical barrier as well. They may influence what we choose to select for antiseptics as well.

In this study, we were just looking at the

effects of the use of a foam product on whether or not there were changes in the microbial counts. We have some evidence from clinical and lab data that these foam products, with or without an antimicrobial ingredient, may also reduce the transmission of microbes between people, probably by reducing skin claim shedding, but also by creating not just a chemical but an actual physical barrier.

This is a study that we did in the 1980s that compared -- Dr. Leyden mentioned this. This is the percent change in skin condition based on several measurement tools that we used. This happened to be the subject assessment. We also use transepidermal water loss and others.

We were able to show significant differences in skin condition, depending on what product was used. In this protocol it was 64 subjects who used a health care personnel hand wash protocol 24 times a day for a week, and even with water we saw some skin damage. In fact, this was a regular bar soap. This happened to be a chlorhexidine gluconate. This was an iodophor. This was a second iodophor.

We were able to show that, even in this fairly intense protocol of 24 washes a day for -- under observation in the lab for a week, that some of the antiseptic products were, in fact, actually in this case better than the bar soaps, significantly better than the bar soap, and this antiseptic product containing povidone iodine was significantly worse. This one, in fact, never made it to market.

Here's some recent studies, one of which is published, and the second of which is in press, just to look at the effect of various -- to look at the correlations between hand washing practices and skin condition in a group of nurses.

In the first survey, basically, it was a prevalence survey to correlate skin damage on hands of nurses in four hospitals, two in this area and two in the northern U.S., actually in Ann Arbor, Michigan. We did it during the winter, because we were interested in whether we could sort out any effects of weather as well as hand washing.

We had 410 nurses in this study, all of whom worked essentially full time in acute care. We

assessed skin damage with several techniques. We used a visual examination under a magnifying glass. We did self-reported questionnaires. We had a dermatologist consultant. We did a lot of psychometric work to make sure that we were getting reproducible results that were valid, etcetera.

We excluded all those with any diagnosed dermatologic problems such as eczema, atopic dermatitis, etcetera. These are just normal nurses working full time.

What we found is that, much to my surprise, about one-fourth of the nurses had measurable, current irritant contact dermatitis, much higher than I would have guessed.

Most of them reported that at some point in the immediate past they had had some serious problems with their skin, and the damage was not correlated in this study with age, sex. All but, you know, a few of them were women, and most of them were working age, between 22 and 45. So there wasn't a big spread in age; skin type, light skin, darker skin; soap use at home; duration of hand washing or glove

brand.

These are the correlates of hand washing. The type of soap used at work was a significant predictor. Chlorhexidine gluconate containing products in this study, interestingly, was significantly less often associated with skin damage than using just a plain soap or a detergent, and the most damaging were the other antimicrobial detergent based products that were used, and in this case it was primarily a PCMX based product. So that was the one that had the most association with skin damage.

There was a significant correlation, as you would expect, with frequency of hand washing, frequency of gloving, and study site. When we did our logistic regression analysis, the independent correlates of skin damage that fell out after all these things were put into the equation were only two, the soap used at work and the frequency of gloving.

We did a follow-up survey that's now in press, and what we wanted to do here was to compare the microbial flora of hands of nurses with healthy and damaged skin to see is there a correlation between

skin damage and skin microbiology.

So we took 20 of the subjects that had been identified in the first study with skin damage and 20 with healthy skin, and we looked -- we did prospectively now a look over a period of three months at their skin practices, their skin flora, and skin condition.

We did, as I said, a prospective data collection for three working weeks over a three-month time period. Subjects kept a detailed diary of their hand care, every time they washed they hands, etcetera. Skin condition was scored by the methods that we used before.

Hands were cultured with the usual gloved use technique after hand washing, immediately after hand washing, and we monitored by having -- We paid a couple of data collectors essentially full time to monitor compliance with the diary so that we were sure we were getting good, solid information on skin practices and hand washing practices.

Again, the microbiologic methods are exactly what you would expect. Some of the results:

The mean hand washes per hour prospectively, as recorded as they're being done, was two. That means that somewhere between 15 and 30 hand washes per shift are occurring.

About half used a nonantimicrobial product. The mean glovings per hour was 1.3. Most of the nurses used powdered gloves only, and the vast majority used hand lotions, which is again a concern that I want to alert us to.

For example, in this study, as you see, essentially everyone but one, I think, used hand lotion. In every case, they were using a chlorhexidine gluconate product that was incompatible with the hand lotion that they were using. So that the hand lotion was neutralizing the effect of the CHG.

This is another consideration now for the use of antiseptic products. It's well known in the literature that, with CHG products, it's necessary to use non-ionic hand lotions rather than ionic, but the ubiquitous hand lotions in the hospital are anionic products.

So, basically, health care workers are using an antiseptic product, thinking that they're getting the efficacy of an antiseptic, and neutralizing the results. So that's another big concern.

This is hard to read. There was no significant difference in the mean colony forming units on the undamaged hands -- the mean log was 5.63 , -- or the damaged hands. So there was no difference in the quantity of flora among those with damaged hands. However, there were a larger of isolates per sample. So that per sample there were an average of about six on undamaged skin, eight with the damaged skin.

Our power, as you can imagine, because we only had 20 per group, was very low here. So my sense is that some of these nonsignificant results would have been significant if we had had a larger sample size.

In terms of the flora, twice as many nurses with damaged hand were colonized with staph homines. Don't ask me what that means clinically. As

far as I know, it doesn't mean a lot except that staph homines is known to be associated with dry skin. So you would expect to see it more.

Then twice as many were colonized with staph aureus. Twice as many carried gram negative bacteria, enterococci and candida among the damaged group as compared to the undamaged.

In terms of comparisons with previous studies, these are just some of the studies that we've published over the years. A group in 1986 of oncology nurses, the mean colony forming unit over a period of about a year of colonizing flora was 4.79; in '92, a group in Peru, 5.74; and in this current study 5.61.

So there doesn't seem to be any significant change in the quantity of flora. Resistance to methicillin -- and you'll kind of have to follow through. The power point didn't come out the same as the slide, but in '86 with 50 isolates, 68 percent were methicillin resistant. This is coagulase negative staph.

In '88, 81 isolates, 50 percent were resistant, etcetera, etcetera. The point again is

that it does not appear that the resistance to methicillin among the staphylococcal flora of nurses is increasing.

Interestingly, the resistance to the flora to tetracycline was actually lower. In our current study only ten percent of isolates were resistant to tetracycline, as compared in the past with anywhere from 23 to 47 percent. No increase in antimicrobial resistance over the past decade.

What we concluded was that efforts to improve hand condition are warranted, because skin damage is associated with changes in the flora, and they're not in the right direction; that efforts should include monitoring of hand care practices, adoption of protectant products in policy protectants such as barrier creams, etcetera; increased use of powder free gloves; and so forth.

Now I do think that the adoption, which we're seeing now in clinical environments, of some of these protectant hand lotions may have a significant clinical effect on even perhaps the efficacy or, certainly, other attributes of some of these

antiseptics, and may have some implications for our testing.

Let's have the lights, and I did want to just end by making a couple of comments about the monograph, as I was asked to make comments about perhaps some of the testing issues.

I'm not going to go over the monograph in detail, because I did it in 1994, and my stuff is there, just like hundreds of other people's were; but I wanted to make three comments.

First of all, the wash protocol for health care personnel hand wash, in my opinion, is not -- I'm now speaking as a clinician. It's not at all realistic. Nobody washes their hands for 30 seconds. If we can't test with the way the products are actually going to be used, and in fact that is outside label requirement -- I mean, that is outside directions on the label anyway.

So why don't we test products for the way they're actually used, which is ten to 15 seconds or not at all. Nobody washes their forearms 40 times a day. Why even bother to -- Those are just minor

little things, and there are a lot of little things like that that really have an impact on the clinical relevance of the testing.

Second concern, major concern, is that the labelling section assumes that there will be health care personnel hand wash products used without water, i.e., alcohols, but the testing protocol doesn't address how you're going to test those at all.

So how can you assume -- What I read from that is there's an assumption of efficacy as a health care personnel hand wash, and yet there's no protocol to test it. I think that's a major problem.

I really fear that, while I've been one of many, many advocates for the need for controls and standardization, it just isn't quite the right balance between flexibility and clinical relevance and standardization. Somehow it doesn't quite meet it yet.

The main thing I'd like to say in conclusion, however, is I'd like to suggest that this whole titling of health care personnel hand wash products is outmoded and inappropriate, and we really

need to rethink the whole thing for two reasons.

First of all, could we think about changing the definition away from a focus on the provider or the person, the user -- that is, the health care worker -- to the risk category; because it seems to me we've heard a lot of evidence, which I agree with, this morning that there are people, whether or not -- no matter what their work site, who are in need of using this kind of an antiseptic product.

Sometimes during outbreaks in daycare centers they ought to use it. Food handlers perhaps ought to be in the same category or certain types of food handlers, anybody who is working in an area where there's a high risk of contamination of the hands.

So my suggestion is that we -- I think we've made too many categories, and we've made it too complicated, and maybe we don't need food handlers antimicrobial wash -- Maybe we need that. I could argue there, but health care personnel hand wash. Why are they different than a daycare provider during an outbreak?

You know, people are not in the hospital very long. The spectrum of care is so wide that you've got people who would have been caring for high risk people in a hospital now in the home, now in the long term care facility.

So I think we would be doing the marketplace a great favor if we got away from the focus on the user and focused rather on the risk situation, and made our title different.

The second area where I think it's a misnomer is the idea of wash. So it's health care personnel and hand wash. Obviously, we're talking about some products that you use with water and you wash, and some products that you use without water and they're not washes.

So the whole titling, I think, needs to be rethought. Thanks.

CHAIRMAN BRASS: Thank you. Questions, comments from the panel?

I have two questions. First, something you pointed out at the beginning that came up at an earlier presentation was the immediate versus delayed

neutralization and impact on the testing.

Could you just clarify which is currently within the TFM standard, and which you think is the most relevant for testing?

DR. LARSON: Well, which is in the current standard? Delayed? Well, I don't know, but --

CHAIRMAN BRASS: I think it is delayed.

DR. LARSON: But we use immediate.

CHAIRMAN BRASS: And why is that?

DR. LARSON: For the same reasons that were discussed this morning, because in our -- Early -- and I started doing this in the 1960s and '70s, and the early stuff we did similar to that, and in fact we did publish a paper years ago -- I think it's from 1968 -- to show that there was a significant difference if you used delayed or immediate; and I mean, also -- I have to say, this whole inoculation -- As somebody mentioned, too, the Serratia on the hands, you can manipulate your testing within the TFM as it's written now in ways that can significantly change the results you get.

I have a real problem with that technique,

because just by rubbing versus drying or just by the amount of pressure -- and we actually even published a paper on this. By the amount of pressure that you use when rubbing through the glove or the bag, you can make a significant difference in the numbers of organisms you get.

So it's an extremely, extremely touchy thing, and particularly when you're inoculating organisms on a living person.

I just want to say one other thing about my concern. We can't get the Serratia off when we're finished, and we stopped doing that technique, because our volunteers, we didn't feel, were safe. Even after four, six hours, soaking in alcohol, we still had Serratia marcescens on our hands, and we didn't feel like doing it anymore.

CHAIRMAN BRASS: Again, I understand there's a difference between immediate and delayed in the results, but which do you think is a more appropriate --

DR. LARSON: Immediate.

CHAIRMAN BRASS: -- for the clinical

relevancy, if this is a surrogate test?

DR. LARSON: Immediate, because you're not -- What you want to do is test what's on the hand when you take it off.

CHAIRMAN BRASS: Okay. Thank you.

My second question goes to your last point, the expansion of the health care to other risk groups, and your points are well taken. But coming back to some of the issues the panel, I think, will be discussing the rest of the day is how comfortable are you in the surrogate marker of kill or decrease in colony counts, extrapolating from a health care validation model to other situations, and then all the way to the consumer use how do we use the surrogate across that spectrum?

DR. LARSON: Right. Well, of course, that's the bottom line question, isn't it, for all of us. I have to say, I was impressed with some of the risk modeling, and I thought in some ways that that may be a step between the kill, which -- the clinical relevance of that is iffy, in my mind.

You got to have it. It's necessary, but

is it sufficient? I'm impressed with some of the modeling. I think that takes us a step further. I think that there's got to be a compromise between nothing, just depending on kill, and the randomized clinical trial for every single new agent that we're trying to put on the market.

So I would agree with some of the things that Jim said, that we have some evidence out there. I do think, however -- and that's one of the comments about cost/benefit -- I'm not sure that we have the evidence that for the general consumer use, but that's not what I was asked to talk about, which I didn't.

For general consumer use, what is the cost/benefit ratio? There is evidence with Triclosan that resistance does occur. As far as I know, there is no evidence that you can -- that the organisms can develop resistance to the alcohols.

So I don't have any concern about the alcohols. I think that there is a concern with antimicrobial resistance with ubiquitous use of these products by consumers over a period of years. I don't think that's resolved.

CHAIRMAN BRASS: Thank you very much.

Our next speaker is Dr. Dennis Maki, Head of the Section of Infectious Diseases, University of Wisconsin Medical School, who will be talking about patient preoperative skin preparations.

DR. MAKI: When we consider enormous advances that have been made in health care in the last 30 years, I think it's quite astounding to many of our patients and the lay public at large that infection is still a serious problem, and the problem of institutionally acquired infection has become ever more complex over the last 20 years.

We've had a tremendous increase in antibiotic resistant hospitals. Nearly 50 percent of hospital acquired staph aureus infections now in hospitals over 500 beds are resistant to methicillin. We've lost the battle there.

Strains of enterococci resistant now to vancomycin and ampicillin pose us with the very first microorganisms that are resistant to all commercial anti-infectants, and we're using experimental drugs for therapy.

Now I've been asked to address the issue of preoperative site care, and I also want to include in that the issue of vascular access. If we look at surgery, nearly 30 million patients undergo a surgical operation in this country every year. About two and half percent, based on this data, will develop a surgical site infection.

This translates to nearly three-quarters of a million surgical site infections a year in the United States. This is the second most common nosocomial infection. It's the most common infection in surgical patients, and it prolongs hospital stay seven days on the average, and adds at least $3,000 to hospital charges.

This is the most sobering statistic. Three-quarters of all deaths in surgical patients in the hospital are related to a surgical site infection.

Now if we consider the issues that are involved in the genesis of a surgical site infection, obviously, the patient's immunity, the skill of the surgeon, but the bottom line is that most surgical wound infections are determined at the time that the

patient is wheeled out of the operating room.

It is the number of microorganisms that have gained access to that wound intraoperatively, and if we simply look at stratifying types of surgery by the likelihood of intraoperative contamination by the patient's own flora, clean orthopedic or neurosurgical or cardiovascular procedures as contrasted with cutting across the stomach -- it has a modest flora -- as opposed to cutting across the colon which has an enormous flora, the rate of infection is directly related to the likelihood of intraoperative contamination.

When we're talking about clean operations such as having a coronary bypass procedure, having a sternotomy, infections here are almost exclusively of staphylococci, skin staphylococci and, increasingly, coagulase negative staphylococci that are almost invariably resistant to methicillin.

It's quite sobering to realize the density of the cutaneous microflora. Dr. Leyden has really devoted his life to studying this area, and I think that some of his studies showing the ubiquity of

staphylococcal colonization are really very impressive.

This is a study that we looked at cardiac surgery and cardiology patients, and we can get nearly 4 logs of organisms off the anterior chest of a patient on admission to the hospital, culturing 25 square Centimeters in a sterile template.

This remains absolutely stable throughout hospitalization. Now let's take the patient who goes to the operating room, has an open heart procedure. The day or two following surgery, there's been a significant reduction in the log numbers, but it's not that great a reduction in the log numbers, illustrating that all of these agents used to reduce counts of organisms on skin certainly don't sterilize the skin. All they do is reduce the number significantly.

Everything that we do in the operating room, the whole ritual of antisepsis, is designed to try to minimize the problem of access of organisms to the wound.

Now I'd like to say a few things about the

other area that I think is encompassed by the preoperative site care part of the monograph, and that is vascular access for fusion therapy, administration of drugs, hemodynamic monitoring.

This is not a trivial issue, and it's become very complex, particularly the enormous increase in use of central devices of all types, not only temporary devices but increasingly long term and permanent devices such as cuffed Hickman or Broviac types of catheters or even subcutaneous ports that are now widely used in patients who need chemotherapy for cancer.

180 million intravascular devices of various types are sold to hospitals and clinics in this country every year. What we've learned over the last 20 years is that the single most important risk factor for developing a bacteremic infection with these devices is the type of device we put in.

The risk now is primarily with central devices of various types. By a variety of methods, you can project there's somewhere in the range of about a half million to a million device related

bloodstream infections in this country every year. This is not a trivial problem.

If you look at the microbiologic profile of device related bloodstream infection, we find that coagulase negative staph candida and staph aureus account for probably two-thirds of all these infections. These are skin organisms. But if you do studies where you prospective look at the source of infection, do molecular subtyping between what you get from the bloodstream, what you culture off of the tip of the device or the hub of the device, what you'll find is that skin organisms account for probably two-thirds of all device related bloodstream infections, usually the patient's own flora.

In this study, large trial, heavy colonization at the insertion site was the single most important risk factor for a patient developing infection of the central venus catheter.

If we look at the differences in risks of infection with central venus catheters versus arterial catheters versus peripheral venus catheters, this is a study in a large coma unit. The risk of infection

with peripheral venus catheters now is very low throughout the United States, probably one infection per 500 devices. With arterial catheters it's about one percent. With central lines it's about three to five percent in most centers.

If we look at the number of organisms on the site at the time we decide to prep it before insertion, the risk of infection is directly related to the number of organisms present. The number of organisms that are present on an internal jugular or subclavian access site is logs greater than we might have on the risk of the dorsum of the hand.

Moreover, it's much more likely that we're going to see gram negative rods, staph aureus, intracoccus or yeast.

Now with that background, let's talk about the monograph and critique -- I'll offer my critique. These are the definitions incorporated in the rule for a health care antiseptic or pre-op skin preparation drug product.

Here, I don't think that there's any question but that we would like something that's very

broad spectrum, and I think that it's desirable that it be persistent. Whether we're talking about an operation that might last three hours or five hours or six hours or eight or ten hours, there will be grow-back. There is no question about it.

Suppressing grow-back certainly has to be desirable, because you're not going to stop the operation after three hours to re-prep the edges of the wound.

When we're talking about an intravascular device, that device will stay in place for days, sometimes in terms of long term devices months, but certainly between site care, which may be as frequent as daily, more frequently now in most centers -- it's every second or third day; in an outpatient home care setting it might be once a week -- preventing grow-back is desirable, because grow-back does increase the risk of infection.

Now what are the professional guidelines of organizations as regards preoperative surgical site care and in terms of vascular access? Basically, we have two major guidelines that are available to us.

Could somebody sharpen this for me? I can't really control the sharpness.

We have the guidelines of the American Operating Room Nurses Association and the HCPAC panel of the CDC. For surgical site preparation, they specify -- make specifications about hair removal. That doesn't bear on the guideline. The issue is the antiseptic.

ORNA really does not give much. It's very, very general, and it really doesn't give us much help except it says to be good. In terms of the CDC guideline, it specifies alcohol, chlorhexidine or a tincture of chlorhexidine or an iodoform.

In terms of vascular access, the CDC guideline which is widely subscribed to by centers in the United States and beyond, it specifies alcohol, povidone iodine or two percent tincture of iodine. They discourage the use of antibacterials which probably increase colonization by candida, but based on a single study suggest that a topical iodoform ointment might be desirable on hemodialysis catheters.

Now let's get to the proposed rule or the

monograph. I would suggest that, if we look at the monograph in terms of in vitro susceptibility testing, which I think is desirable because there are differences between organisms, I can't see much point including these organisms: B. fragilis, hemophilus influenza, micrococcus luteus or streptococcus pneumoniae.

The likelihood that they would be pathogens with regard to a surgical site infection related to failure to cutaneous antisepsis is vanishingly small, and this simply adds cost and time.

Although there is no evidence that there are differences in vitro susceptibility between antibiotic resistant organisms and susceptible organisms, the data are rather limited that have examined that issue. Because of the tremendous importance of resistant staph and enterococcus, I think that these ought to be included in in vitro susceptibility assessments of new antiseptics.

I think an anaerobe, however, where failure of cutaneous disinfection has clearly resulted in infection is Clostridium, and I think that

Clostridium -- it would be desirable to include this in assessments.

I would also suggest it might be desirable, if we're looking at antiseptic agents, for instance, to hand care, to look at antiviral activity for Herpes simplex and respiratory syncytial virus, two very important viruses that have been known to be spread widely within hospitals on the hands of health care workers.

In terms of in vitro time kill, I think that this is of some value, but it's very general. We should specify criteria, at least three to four logs in a minute.

Now in terms of in vivo testing and volunteers, I have a lot of reservations about this. I'm not very enthused about studying healthy volunteers. They're not the same as patients. Patients in hospitals might have 6 logs of candida on their chest. They might have huge numbers of gram negative rods, and studying healthy volunteers may not really give us the best insight as to the relative efficacy of one agent as compared with another.

I think we should -- I would agree very much with prior discussants here that we need to examine the criteria in terms of in vitro tests for studies that are done in small numbers of patients looking at efficacy in terms of cutaneous disinfection.

This is what I think, on the other hand, is really needed. I'm, frankly, very disappointed how little good clinical data we have to guide us in what we should do.

You know, if one of us starts having chest pain on the way home this afternoon and they bring us into a center, and we are having an acute anterior myocardial infarction, unless there's a compelling contraindication, your physician is going to give you a thrombolytic. Why? Because NIH has probably spent $100 million over the last ten years studying over 50,000 patients in various trials of different thrombolytics to demonstrate there's a ten percent reduction in mortality if you use a thrombolytic as opposed to you don't.

Well, when we're talking about millions of

serious infections, it's astounding how little good data we have in terms of clinical studies that have told us what is the best agent to use.

I think it's clear that for surgical site care you can use an iodoform. You can use chlorhexidine. You can use tincture of iodine. You can use alcohol. But what if one of them is ten percent better than the other, 15 percent.

Ten or 15 percent reduction in the risk of surgical infection using the best agent would translate to preventing probably 70-80,000 serious surgical site infections every year, and probably save several thousand lives.

It is possible to do these trials. Let me show an example, when I get back to my second point.

For vascular access we're starting to get some data to guide us what we maybe ought to be doing. If we look at cutaneous disinfection before you insert an intravascular device, what's used in most hospitals in the United States is an iodoform.

What's used throughout most of Europe and in Canada is chlorhexidine. Now there's lots of

potential candidates for antiseptics. Most of these are not approved for the indication in the monograph.

This is a trial done simply looking at vascular access, looking at three agents, looking at the gold standard in the United States, iodophorus, as opposed to alcohol. That's very popular in Germany and Austria, and looking at chlorhexidine. That does well in studies.

This is a study where the effort was to look at preventing bacteremia, not looking at what removes organisms from skin more effectively. The bottom line is what protects patients from serious infection.

So patients admitted to a trauma unit who would need an arterial line or central venous catheter were randomized at the time of catheter insertion. Now it was also rather interesting. The study showed that povidone iodine and alcohol were equivalent, with about a three percent rate of bacteremia. Chlorhexidine was fivefold better.

If these data are valid, which I'll show you data to think they are, switching to chlorhexidine

tomorrow on a wide scale in U.S. hospitals would prevent hundreds of thousands of bacteremias in the first year.

Most catheters are put in by the Selvinger technique using a guide wire. This can introduce organisms into the lumen of the catheter. In this study it was possible to demonstrate that the superior antiseptic also prevented infections that were lumenally -- intralumenally acquired.

Here's a similar study in Europe looking at ten percent povidone iodine against a very low concentration of chlorhexidine and a low concentration of alcohol. I would be very nervous about using this agent, frankly, because of the low concentrations of the antiseptics, but again here the harponics are being performed well.

It reduced the incidence of gram positive bloodstream infection 80 percent. This is not the greatest trial, but it gives a trend, which I think is worthy of looking at, and that is it's a large nutritional support program in Europe where they use tincture of iodine exclusively for site care and

disinfection for about three years. They then switch to an iodoform.

They realized they had a twofold increase in invasive infections in the population. They switched back to tincture of iodine, then to chlorhexidine, and came back to their lower level. This is not real strong data, but it's a trend that suggests that chlorhexidine and perhaps tincture of iodine is superior to iodoforms.

The last study I'll show is a multi-center trial done in neonates where peripheral venous catheters are used for access, looking at a tincture of chlorhexidine versus povidone iodine. Again, the chlorhexidine performed superiorly.

I think it's time that chlorhexidine, whether it's an aqueous solution or a tincture, be approved for vascular access in this country. This is not encompassed in the monograph, but I think it is such an important issue in health are, it bears strong consideration.

Dr. Larson could have probably given every presentation here today with the extent of the work

that she's done on skin disinfection. This is a summary of studies that she analyzed in a recent paper that she published that looked at the efficacy of preoperative patient bathing, which bears on our issues today.

We don't have an answer as to whether preoperative bathing makes a difference or not. The major reason is that there have been four trials that have had infection as the endpoint of comparison. Unfortunately, two of them showed a significant decrease. Two of them did not.

On the other hand, there were methodologic differences in definition of infection, the number of preoperative showers that were used, and the answers is unresolved. Yet it is recommended, and most surgeons do use a preoperative antiseptic shower or bath before elected surgery.

We should get better data than this to tell us what should we use, what's the best way to do it.

If we look at surgical site preparations, the situation is even worse. There have been very few

studies that have adequate statistical power to give us any insight as to the relative efficacy of the different agents that are currently approved for surgical site disinfection in surgery.

Most of the studies have looked at colonization. They have not used infection as an endpoint, and there is an awful lot more serious surgical infections and device related bacteremias than there are in myocardial infarctions. We ought to have better data than this.

Antiseptics, I would close by suggesting, have the greatest hope for being able to materially reduce the problem of antibiotic resistant organisms. Incorporating antiseptics into the device itself holds a promise of substantially reducing the risk of device related bloodstream infection.

The challenge is finding the best agents and, particularly, defining where they ought to be used.

Thank you very much.

CHAIRMAN BRASS: Thank you. Comments, questions from the panel? Dr. D'Agostino?

DR. D'AGOSTINO: Could I just try to follow up on an idea of the clinical trial. If you think of the drug approval process, it might be different than the scenarios that you were suggesting where you were making comparative trials.

If you had a drug -- If we suggested, for example, or the panel suggested that the clinical trials really be looked at very seriously for approval, then you wouldn't do a placebo control, obviously.

Is there some standard that could be used for controls to make the comparisons for the approval?

DR. MAKI: I anticipated that question.

DR. D'AGOSTINO: Good.

DR. MAKI: And I thought about it. First of all, I don't think that it's going to be practical or as desirable for the panel to -- if they decide clinical trials are important, to decide that every manufacturer of the agents that are currently approved has to do clinical trials to show they're efficacious.

I think it's clear that the agents that are used do confer benefit, and they're going to be

superior to placebo. There's no role for placebo controlled trials here.

There might be for preoperative bathing. That's another issue, but for surgical site care for vascular access that's not an issue.

What I would suggest, on the other hand, is that, if there's a promising new agent that wants to get into the market for surgical site preparation or for vascular access, it ought to have to have a good clinical trial, a clinical trial that compares with one or more of the currently approved agents.

If it turns out that the clinical trial suggests that the new agent is superior, I can assure you that it's going to prompt further studies of the older agents in the marketplace to try and defend their position in the marketplace; but I think that new agents -- and we certainly need new agents -- ought to require clinical trials comparing with existing agents.

CHAIRMAN BRASS: Thank you. Other questions or comments? Thank you very much, Dr. Maki.

Our next speaker is Mr. John Guzewich from

the Food Safety Initiative at the FDA, who will be speaking on food handler hand wash.

MR. GUZEWICH: Good morning. My name is Jack Guzewich. I work for the Food and Drug Administration in the Food Safety Initiative part of the Center for Food Safety and Applied Nutrition. I've worked there for 13 months.

Prior to that I worked for the New York State Health Department for 27 years where I ran the food borne disease epidemiology program and the retail food program, which is regulations over restaurants and supermarkets and the like.

I also want to comment before I begin that I do not take credit for talking about food borne disease just before the lunch period. I was not the scheduled designer for that little apparent piece of time in there.

What I want to talk about today is our concerns related to this -- See, I had food worker hand wash. You'll learn as I go along here that I have a particular problem with food handler. It's a big concern of mine. I've been a crusader for many

years.

Can I have the next slide, please?

We have to begin on this by looking at the role that food workers, not handlers, have in the epidemiology of food borne disease. Evidence is becoming more and more strong that food workers are probably the -- that's with a capital T -- The major cause of contamination of food in restaurants and other places, rather than the raw animal foods and other things that are sort of dogma in that area.

So I want to talk a little bit about agents, and also about contributing factors, and I'd like to point out here that agents I consider all these three categories: The bacteria, the viruses and the protozoan parasites.

Most education in this area will make you think that bacteria are the major agents of concern, and there's a lot of biases into what has been reported in the past to lead you to that conclusion, but in fact viruses cause far more food borne illness than do bacteria, although not as severe disease.

We're now seeing -- the early stages are

telling us that probably protozoan parasites are also being spread this way, and they will create all kinds of problems in terms of efficacy, if we're going to talk about trying to control them on hands.

I'll talk a little bit about the contributing factors that lead to food borne outbreaks, the causes that have our concerns.

First we'll take a quick look at some CDC data, and these are data that were compiled by CDC through a passive surveillance program. I emphasize that, because we could spend the rest of the day talking about the number of biases in this data.

Nevertheless, the way they categorize this information, you can see that there are -- On the lefthand side of these two tables, the contributing factors are what was felt by investigators to be the errors or the steps that led to this particular food borne illness.

For bacterial agents, you can see, for instance, that temperature in the 73-87 area was -- temperature abuse was involved in 87 percent of the outbreaks.

Well, if we go down to this one called hygiene, which is the fifth one down there, you can see there hygiene. Now hygiene covers a whole range of sins, not all of which are relevant to the day, but they all tie in, were involved in 59 percent of the bacterial outbreaks, 92 percent of the viral, 60 percent of the parasitic and two percent of the chemical; and we get some kind of crazy insights into what all that means.

Then in the more recent period, '88 to '92, we had 34 percent of bacterial, 87 percent of viral, 33 percent of parasitic, and one percent of chemical. So hygiene is a major factor, obviously, in the way they categorize the data.

Now when I was in New York, we developed a system that we felt was a whole lot better than that, and we did report 33 percent of the food borne illness in the country, although we had only seven percent of the population in the States. That's not because food is that much more unsafe in New York. It's only because we cared to look for what was causing the problems.

Could I have the next slide, please?

We get here our way of categorizing the data. We have some biases in here, too. We are particularly plagued with outbreaks associated with raw shellfish and with shell eggs, and those data kind of skew what's up here so that you see they're contaminated ingredients, which relates to many of our shellfish outbreaks and our egg outbreaks.

Consumption of raw or lightly heated animal food: Again, there's a bias because of those kind of outbreaks.

We go down here to infected person, and you can see infected person ranks five on that list; but if we took out the egg and shellfish outbreaks, infected personnel would become one of the major contributing factors to the food borne illnesses we saw over that 16 year period.

Could I have the next slide, please?

If we look at the agents that were involved in those outbreaks, you can see that nonspecific viral gastroenteritis -- and for those of you who are familiar with this phenomenon, you know

that there's not readily available laboratory testing for the Norwalk family, and so you end up with these different euphemisms for what that disease is.

Anyway, that was the predominant agent in our food worker associated outbreaks, and salmonella was second. There you see we had some enteritidis, which people think are just with eggs, but we do get them food workers, too.

Then salmonella typhae: We had a beautiful typhae we could talk about. Hepatitis A, Norwalk virus, rotavirus. Could we over to the next slide, please?

Staph aureus, the one that's near and dear to everybody's heart; Shigella, Beta hemolytic streptococcus was involved in three outbreaks; Campylobacter in one, and Yersinia in one, 27 outbreaks.

We had ill food workers involved, but we were not able to identify what agent they actually had anymore specifically than that. So you can see, we have a host of agents, both bacterial and viral.

We have no parasitic ones on there. We

didn't have that experience, but I can tell you just in my brief time here at CDC, I've been involved in two investigations here in the U.S. where we have reason to believe that food workers were involved.

One parasitic outbreak was cyclospora, and the other was cryptosporidium, and I'm sure that we're going to see more of that as time goes on. Next slide, please.

So the role of food workers in food borne disease is quite significant, and I'm just talking now about the agents that the worker carries when he or she walks into the job in the morning. I'm not talking about the ones that they pick up from the raw chicken and transfer over to the ready-to-eat food. I'm talking about the ones that are carrying in or on their bodies.

We think that is a major source. Our problem in this industry is that people work when they're ill. They don't get paid if they don't come to work. They may, in fact, lose their jobs if they don't come to work. So our economic incentives are come to work, even though you're ill, and in fact,

that's what they do.

So they're going to be there when they're not feeling well, not to mention when they're in some kind of a carrier state. Added to that is the problem that people do not wash their hands. Food workers are not unique in this respect and, when they do wash their hands, they don't do it very well.

You didn't know, but we had the hands police in the bathroom this morning, but I did one of my usual informal, unofficial surveys, and found that even among people who sell these products and foster their use, hand washing is intermittent and certainly not in the duration adequate to achieve what we're all trying to achieve today. This is only in the men's room. I can't speak for the women's room experience in that regard, but I suspect it wasn't a lot different.

So people don't wash their hands, and that's a real problem for us. Could we go on to the next slide, please?

So what is the answer that the Federal government has to the world's problems? Well, in this

area the FDA does have regulations over establishments, companies that prepare food that are sold in interstate commerce, and we have good manufacturing practices and the like.

We also have a document that we don't particularly enforce in most settings, but is a model. It's called the Food Code, and some of you have heard of this document and some of you haven't. But it's a model regulation that we encourage state and local regulatory agencies to adopt and enforce for regulating restaurants and supermarkets and similar kinds of establishments. Health care facility kitchens are included in that, by the way.

So that pertains to what we call retail food, and there are provisions in here that are relevant to the discussions today. One of them is that we say that people may not contact ready-to-eat food with their bare hands.

We've gotten to the point in this issue that we feel -- that was based on our experience in New York state when I was there -- that people are not going to do this the way it needs to be done. So if

we can keep their hands off the food altogether, the ready-to-eat food, that's probably the most effective intervention.

Unfortunately, this intervention isn't agreed to by all parties, as you can imagine, and so in many places in the country, in fact most places in the country, that standard does not apply, because this is a voluntary standard.

So there's going to continue to be a legitimate need for hand wash products and sanitizing products that keep people's hands clean, even if this was in effect, and I'm sure it will never be in effect in all places.

The regulation requires that people's hands be in a clean condition, that they use a cleaning procedure, and we heard earlier about a 30 second procedure. Our Code talks about a 20 second procedure. So if you're going to test these products, obviously, you've got to test them for a duration that's relevant to what's actually being required.

We tell them when to wash, and we define all the times when hands would be contaminated as to

when to wash. We talk about where they should wash them, meaning a hand washing sink as opposed to the sink above where they are washing off the lettuce or something, and we talk about hand sanitizers.

Hand sanitizers are important in here, because we say that hand sanitizers should be used on clean hands. There are products in the marketplace today that are purporting to be used anytime you need to use them periodically, and we have retail establishments that have people periodically applying these compounds when they haven't got time to wash their hands.

Well, if they haven't washed their hands to remove the soil, then they negate what we say in our regulation. I'm sure most of you would agree with, that if you don't have a clean area to sanitize, then sanitizing isn't going to do you a whole lot of good.

If I can have the next slide, please.

We have some other concerns in this area, and I sort of alluded to some of them already. First is emerging pathogens.

Emerging gets to be kind of a word, whichever fits, but some people consider viruses to be emerging pathogens. I don't really think they're emerging. They're just maybe not being recognized by everybody for a long time, and I don't know how we address viruses here.

We've heard already this morning by some of the scientists that these agents, cleaning agents and sanitizing agents, may have effect on viruses. Whether they will affect all these enteric viruses or not, I don't know. What effect they have on parasites may be even more problematic, and we are seeing the pathogens coming along with some characteristics that cause us some real concern.

E. coli 015787 is an organism that is particularly acid resistant. Now our microbiologists, when I discussed this testimony today, said, you know, we're not really sure whether this acid resistance is in anyway related to more resistance to sanitizers or not, but it's a concern of theirs.

There's a bug out there right now called Salmonella typhaemurium DT104 that is a multiply drug

resistant salmonella that causes infection in animals as well as in humans, and an organism like that that is multiply drug resistant to antibiotics -- whether that relates to hand sanitizers, we don't know.

So emerging pathogens are a concern, and they're going to complicate the whole spectrum of this subject.

Also we have food additive requirements, and I'm going to allude to some of these things more than once. We have requirements in the FDA that things that are going to be in contact with food have to meet food additive requirements.

Well, that includes hands. So these sanitizing compounds that are on people's hands in theory can be transferred to the food. Therefore, they become food additives. Therefore, they have to comply with food additive requirements and concerns as well as all the others, and let me tell you, that's going to make life a little more complicated.

Next slide, please.

Attributes: Speed of action -- As I mentioned a minute ago, our regulation talks about 20

seconds, which is what we recommend as the duration. Those of you who don't want to use a stopwatch, one stanza of "Old MacDonald" works very well to get you to about 20 seconds. You can try that the next time you're in the restroom.

Indicators versus pathogens: Our microbiologists are a little bit concerned about this one. We know that there's a lot of very good reasons why you want to use indicators rather than the actual pathogens, and those are certainly important reasons.

We're not sure that there's enough information there to show that you can always have an indicator necessarily truly represent what the pathogen is going to be like. So we're going to have to have some way of having confidence that the indicator represents all our concerns about the pathogen before we can make that leap of faith.

Then we have low dose agents. From the information I've seen today and information I saw at a meeting that CDER held last week, these agents typically are expected to reduce the loads on hands maybe by one log or two logs of organisms.

We have a real problem here. Some of these agents we deal with in food borne disease are low infectious dose organisms, and salmonella typhae fits in that category. E. coli 0157 probably has infectious dose of ten organisms or less. Coli is down there. Shigella is down there. The viral agents are down in that area.

So we have agents where you don't have to have a whole lot of them on your hands to make people sick. So it gets real complicated what kind of claims we can make about these products in light of those low dose organisms.

Next slide, please.

Attributes: Well, we have, first of all, spectrum of action, and what kind of claims can be made about organisms, the organisms concerned? Are they the bacteria, the viruses, the parasites? What do we say about those kind of things? What kind of claims can we make about addressing all those different organisms of concern?

Then we have this resistance idea that I've already talked about. Will these organisms show

resistance? Will the more emerging pathogens, in particular, be a concern when they have acid resistance, when they have multiply drug resistance already being demonstrated?

Next slide.

Length of action: Does persistence, which is a great characteristic on these products, also make them more likely to be a food additive issue? I suspect -- I don't know. I suspect in some cases those may be working at cross-purposes, and that issue is going to have to be addressed if persistence, by its very nature, means you go into the food additive requirements.

Next slide, please.

The last slide I have is on the issue of soil, and I think that this gets real complicated. Soils that occur at the retail level are likely to also show up at the processor level. I don't think that you can necessarily say that people who are working in the processor's situation are necessarily going to have hands that are anymore soiled than you have at the retail level, because these days retail

level does everything that goes on at the processor.

They're doing the whole spectrum of activity there. Also, you've got to -- I don't have it right here on the slide, but we also have to worry about a category that I haven't heard addressed yet today, and that's in the agricultural environment.

We have veterinarians who use hand wash products. We have other workers. We have people that work in milk houses that use hand wash products and then milk cows.

Also now, those of you who like to eat produce, and that would be some people in the room who do that, maybe are aware of our big concern in FDA about food borne illness associated with produce. We don't really know where the produce is becoming contaminated.

One of the possible sources is the agricultural workers in the field, and do they wash their hands or not; and if so, what do they use to wash their hands with and sanitize their hands with before they pick that produce that you may or may not cook before you eat?

With all those troubling thoughts, I'll be happy to answer any questions.

CHAIRMAN BRASS: Thank you very much. Questions or comments from the panel? Dr. Maki?

DR. MAKI: An observation and a question.

First of all, to open the enormous barrel of worms of considering cutaneous antiseptics used on hands as an additive, then you better start getting ready to do that with all cosmetics and every other thing that you put on people's skin that people get on their hands, and they feed themselves. They use their hands to feed themselves.

I think that that's opening a huge pile of pain that may not be justified.

MR. GUZEWICH; I hear your point. All I can respond to is that it's --I mean, it's a fact. The food additive requirements have to be applied in these areas, and cosmetics -- I think those issues are addressed to some extent, but when you come out with a product that's specifically designed to be put in contact with a person's hand who in turn is going to be preparing food, you've opened yourself up to the

food additive regulations.

When you're talking about a cosmetic that has that more indirect relationship, I'm not sure that food additive requirement applies, but it will apply in these situations, and I know it's going to complicate the issue.

DR. MAKI: And you're talking about hand lotions and all kinds of skin care products.

The question is: I've come to sort of look at the hands, the skin of the hands, as being a big sponge, and it attracts organisms, and once you put them on, exactly as Elaine pointed out, I think, you know, contaminating hands with Serratia is very artificial.

I'm not sure it tells us very much, and I agree completely. Why should you colonize a small set of the people permanently with a virulent gram negative rod if they're going to be health care workers someday.

The question is why not require all health care workers to use disposable gloves? I would think that that would be the logical way of making it

convenient to eliminate this issue of organisms they may have in their hands, because they're incubating hepatitis A and they have ten million virions on their hands that you're not going to remove with a three-minute hand washing, but gloves, I think, might have the greatest hope for preventing food borne illness.

MR. GUZEWICH: You and I are of like mind on that, but that is not a universally held belief. people don't like to wear gloves. They see a lot of objections to gloves. They feel they should have the right to have an effective hand wash in lieu of.

That's a very hotly debated area in the area of food safety right now, is whether prohibiting bare hand contact, which oftentimes relates to using gloves, although we out in the lobby use deli papers, tongs, spatulas. There's many things you can use other than your hands to do certain activities, but there are activities that, practically speaking, you're going to want that hand tactile aspect, and gloves are going to be involved.

We had this requirement in New York. We adopted it in '92. We've had a heck of a time getting

compliance with that, but I can tell you -- and I'm involved in a bunch of epidemiologic work on this right now -- that there continue to be food borne outbreaks in the United States associated with ill workers who have bare hand contact with food.

In our tracing these things, we did not have outbreaks in situations where people were not touching the food and they were wearing gloves. It's that simple.

Now one of the things that's thrown back at us that you health care people know much more about than we do in the food area is that, when you have a glove on for a long period of time, you've got all kinds of things going on underneath that glove, too.

These are all the issues that you deal with in the health care saying that we're being thrown the same ones in the food sector. The difference is there are tomes' worth of studies that have been done on this in the health care setting.

As was brought up earlier, how much of that can be related over to the food setting? Is it appropriate to relate those over? Are they the same

agents? Are they appropriate to be thought of in the same way? We don't have all those answers right now.

CHAIRMAN BRASS: Dr. Larson.

DR. LARSON: What's the rationale for the 20 second hand wash, and what's the evidence of compliance with that? Do people really do that?

MR. GUZEWICH: I'm not sure whether -- I could find out for you where the rationale --

DR. LARSON: I mean, it's more stringent than health care workers, and I understand, you know, that they ought to be stringent, but --

MR. GUZEWICH: I don't know the answer to where that 20 second -- I could look that up for you.

As far as compliance, we have ample anecdotal evidence to suggest that compliance is not very high, and that's our problem.

DR. MAKI: See, where it's probably important for the food worker, more important than anything, is that they wash their hands really vigorously after they go to the bathroom.

MR. GUZEWICH; Absolutely.

DR. MAKI: We've studied organisms on the

hands of health care workers and non-health care workers, and it's very interesting. They both carry about the same amount of staph aureus.

The health care workers carry lots of methicillin resistant staph epi. which we virtually never find on the hands of non-health care workers, but when you look at the gram negative rods, the total log count of gram negative rods are about the same in both groups.

In the health care workers there's Kebsiellae, interbactus, Serratias, pseudomonas or hospital resistant gram negative rods. In the non-health care workers we almost never see those organisms unless they have a job that has them in wet work a lot. Otherwise, it's all e. coli, and you know where that came from.

MR. GUZEWICH: Yes. I'll point out to you that, although we have a difficult time getting compliance with hand washing in this country, at least a lot of people here know that's an expectation. We do have people working in this industry who come from places where that's not an expectation.

CHAIRMAN BRASS: Yes, Dr. Neill?

DR. NEILL: Having taken my daily dose of Triclosan this morning in the form of toothpaste, which is now on the market, I'm pleased that somebody is interested in determining the extent to which the entry of these types of materials into the food chain is going to affect my health or that of my children or those of my patients.

That aside, this whole food handling issue seems prone -- engenders an important question for me, which I'm not sure I heard an answer to.

One is the testing that has been proposed as a surrogate to clinical trials for non-food handlers does not have, it would seem, except in the epidemiologic data and the case data that the various public health departments generate -- doesn't seem to have an equivalent, and I'm looking for an answer to you as to whether you feel the proposed surrogate tests in the monograph from '94 in any of their forms are reasonable to use in the food handling preparation category.

MR. GUZEWICH: I don't know the answer to

that, because it hasn't been tested that way. That's the whole problem. We rely on epidemiologic information. There has been a certain amount of -- There have been a few studies of hand worker -- food worker hands. Okay, there hasn't been none. But there's relatively few -- a small body of science in that area.

So the question that we are struggling with is how much of that information from the clinical experience and setting can be translated, and we don't have a good way to analyze that. Anything this panel can say in that regard would be very helpful to us, because we don't know what to make of it.

We're very much embroiled in this issue of food worker hands, and should they be prohibited from bare hand contact or is hand washing acceptable or is hand sanitizer acceptable or some combination of that?

We have some very strongly held opinions on all sides of that. The industry doesn't always agree with us on this issue. The food service industry, I'm talking about now, and the retail food industry.

We're looking for the science to base our decisions on, and the earlier speaker was here on microbial modeling. The FDA under the Food Safety Initiative, one of our major thrusts is to get more into the area of microbiologic modeling of food borne disease and to look at that in terms of maybe coming to the decision making process and the whole risk analysis system.

So we're looking to go toward that way and to have the scientific data upon which to make models. Our problem right now is there's so little data that you can't even begin to design your models, and our scientists are scratching their heads, desperate.

We're going to be paying people all kinds of bizarre things to get some basic data so we can develop models. So I don't have a good answer, because we're asking the same questions.

CHAIRMAN BRASS: Dr. Maki?

DR. MAKI: I would just say again, I think the evidence in the health care setting, and particularly the greatest challenge for preventing spread of organisms that are transmitted on hands, is

in the hospital critical intensive care unit.

There, barriers -- Pretty good data indicate the use of barriers where people don't touch with bare hands significantly reduces transmission. There's data, certainly, in epidemics. There's endemic data that suggests that is beneficial.

I, frankly, think that trying to improve compliance in an industry where people are already stressed to the max and they're going to continue to work when they're ill, I don't care what you say -- it's going to be hard to get them to wash their hands more than ten or 15 seconds, if they wash them frequently enough.

I think finding a way effective to use barriers, whether they use instruments or they use gloves -- I don't think food workers should touch or handle any food that's not going to be cooked well after they handle it.

MR. GUZEWICH: You're right where I am on that subject, and barriers is the word we use; but I also would like to suggest that you would agree, I'm sure, that we still would like surgeons to wash their

hands before they put the gloves on; and we feel the same way about food workers. They should still be washing their hands even if they do go to the barrier method.

DR. MAKI: The use of barriers is not a means to discourage hygienic hand washing where it should be done.

MR. GUZEWICH: To pick up on that phrase, I mean it's multiple barriers. Ideally, they shouldn't be coming to work if they're ill, and then they would not -- then they would be washing their hands as well, and they would have the barrier. We would have three barriers in place.

Our problem now is that we can't get compliance on any of those barriers.

DR. LARSON: Well, I'm just not convinced that there's any evidence that 20 seconds is a magic number, any better than 15 or maybe even ten. The problem, when we make rules that are sort of -- the attitude is, well, if ten is good, 20 is probably twice as good. That's not true. We all know that.

So people -- The unrealistic rules make

compliance even more impossible, because if you count 20 seconds, it is forever, and it just is almost like if we under-rule rather than over-rule, we'll have perhaps less problem with compliance, because people then blanket say, well, this is not doable.

MR. GUZEWICH: Your point is well taken, and like I told you before, I do not know specifically where they got that number 20 seconds. I will try to find that out and get back to you on that, but if this group could give us advice in that area and feel that some other duration would be better, we're open to all kinds of input. We always want input on these kind of things. We really do.

DR. LARSON: Yeah. There are good data from Wenzell that do show that ten seconds is probably equivalent to 15 at least. I don't know about 20.

CHAIRMAN BRASS: Thank you. It's now Noon. I know this has made me hungry. It's lunchtime.

I'd like to reconvene promptly at one for the public session, because we have scheduled peoples.

Thank you very much.

(Whereupon, the foregoing matter went off the record at 12:03 P.M.)

- - -

AFTERNOON SESSION

Time: 1:02 p.m.

CHAIRMAN BRASS: If we can start to reconvene, please.

Our next series of speakers will be those who have requested time in the open public hearing. As I introduce each of the individuals who will be speaking, I would request that each of them identify not only their current affiliation but any sponsorship for their activities today and any conflicts of interest that they feel appropriate to disclose to the panel.

Our first speaker will be Dr. Abdul Zafar.

DR. ZAFAR: My name is Abdul Zafar. I work in the Arlington Hospital, which is 15 miles from here, and is a 450 bed acute care teaching hospital, and I there for the last ten years managing the infection control department.

I am here to present our findings of a study of the request of industry. This is the hospital I'm talking about.

We had this outbreak of MRSA, methicillin

resistant staph aureus. We don't expect these infections in the nursery, and so when we saw the first case, we had great kind concern.

This is the whole outbreak. We never saw that infection in the nursery, as I told you, but it was there. We see infections in generally 1990. There's the first or index case. Then we see all these infections.

Because of the severity of the infection, literally I moved my office to the nursery, and we did many things to control that outbreak. All the infections were in the male infants. So we are looking at what different things we are doing for the male infants, and these are the different methods we took in the month of February.

Everything is still exploratory. Even then we kept on seeing this outbreak. Then in April we made a change in our hand washing policy and the infant bathing policy. The changes: To institute Triclosan 20 percent for infant bathing and hand washing.

Although we did not have an -- of use of

2.3 percent Triclosan in the infant, but we had to take the chance, and soon after that change you can see the change.

Since then, there has been no MRSA infection in our nursery.

CHAIRMAN BRASS: Does that complete your comment?

DR. ZAFAR: Yes.

CHAIRMAN BRASS: Are there questions or comments from the panel? Thank you.

Our next speaker is Paul Marshall, and again if you could identify your current affiliation, any sponsorships or conflicts of interest, please.

DR. MARSHALL: Good afternoon, ladies and gentlemen. Thank you for the opportunity to come here to present the results of some findings that we did on research on reducing MRSI using Triclosan.

The first thing I'd like to state is that, although I am here sponsored by the trade, the interesting thing with this research was that the companies whose products were used in it didn't know what was going on, and I had the absolute fabulous

pleasure of watching the national sales manager for both Johnson & Johnson and Reckett & Colman have their mouths drop wide open when I presented the paper.

Why is somebody from the Antipodes is up here talking to you, august body over here in the states? I am an infection control consultant. I have been for the last eight years, and prior to that I was actually working at St. Vincent's Hospital in Sydney where I ran the MRSA isolation unit.

That ward was probably the most difficult challenge that anybody could look after, because we used to look after any patient with MRSA, whether they were a heart/lung transplant, heart transplant, burns, bone marrow transplant, you name it. Whatever came across the door and got infected, we got.

It really got me quite interested in seeing what was going on with MRSA and ways that we could actually reduce it. Currently, I'm working at this gorgeous little hospital called the Sutherland Center for Nursing and Medical Excellence. It's situated on the southern extremity of Sydney and right in the middle there is the actual city of Sydney.

It's about 25k out of the city itself.

All of us are worried about infections in hospital, and the way that those infections impact on our patients, and that's the basis for any clinical investigation, is what happens to the patients themselves.

Bugs are sneaky little things. You can have one sitting there, anywhere. Any opportunity for it to get in, and it will take hold, then operate like rabbits. And what do we get at the end of it? Anything. It can be a cellulitis for a patient.

Infection can actually cause damage itself and cause ulcers or it can infect iatrogenic problems such as pressure areas. This is my pressure area, because all of them are connected.

It can also affect very, very unusual conditions. This is a patient with an unusual manifestation of mycoses fungoides, and with mycoses any irritation on the skin itself will end up with another lesion coming through. So treating this patient, who is heavily colonized and infected, actually, with MRSA and pseudomonas, we had to be able

to try and find something that was very, very low irritant to treat him.

It also affected his legs, and the one on the righthand side -- that channel actually went right through to the other side of his foot.

It causes surgical problems. Infected amputations can take forever to heal because of the impaired vascularity. Patients can have small pressure areas which actually get infected. In the case of this patient, we actually asked the plastic surgeons just to clear it up a little bit for us, and they just kept on cutting and cutting and cutting and cutting.

This patient, by the way, had no elevated white cells, no increasing neutrophil percentage, no temperature whatsoever, but that was the condition of his foot.

It can cause problems such as necrotizing fascitis, in this patient who came in for just an open and close laparotomy of CI of the stomach. It can cause beautiful problems when you've got any vasculature artificial graft done, such as in this

patient with a fem fem crossover graft; or in a worse case scenario, this patient who, unfortunately, had a fem fem crossover graft performed which got very, very heavily infected with MRSA, infarcted one leg, and we actually had to slice through the leg to try and save her life.

All of those patients had MRSA. None of them died from MRSA. If they died, it was due to their underlying problems, not infection. That is one hell of an achievement for any hospital to state, that we were able to control and contain infection to the point where it did not cause mortality. May have contributed to a morbidity, but definitely not mortality.

The problem is with MRSA in other patients or other organisms is what are you dealing with. You only know if you swab someone. The only way you can -- most hospitals look after MRSA is trying to identify patients with a positive isolate from routine swabbing and institute some sort of treatment for those, but that's not really good enough; because what about those that you don't know about.

We did investigations to find out roughly how long it was from the time a patient was instituted -- admitted to the institution -- that's better -- to actually showing the first signs of MRSA and colonization swabbing, and it was 13.4 days.

So we're saying that that patient had a hospital acquired MRSA, because it was 13.4 days after they came in or just we didn't swab that one particular place? The only way you can find out, really, if all of your patients do have multi-resistant organisms is if I got everyone of you, if you were patients of mine, stuck you in a vat of media, ask you to breathe three times and pass flatus. Then I could effectively say you did not have MRSA carriage.

To try and treat everybody -- why not treat everybody? Treat the pool. That way you get rid of cross-infection. So that's what we wanted to do, to try and work out a way that we could treat all patients in the hospital to reduce the potentiality for getting MRSA, but there are many, many factors come into play with MRSA, and things that can change

what you're looking for.

Were there alterations in the skin preparation used in the theaters? Were there changes in hand washing solutions or hand care solutions? Were the cleaning products going to be changed? Did the cleaning protocols have anything to do with the patients itself? What about antibiotic usage? Were they consistent? Did they change?

We tried to work out a way that we could look at one variable and one variable alone, and that was introducing Triclosan body washing.

We brought that in in the form of Microshield T as a body wash solution for all patients, if they were bedfast. They were given their own supply and now washed with that or booked admissions for surgery were asked to buy Sapoderm soap, to have two preoperative washes before they came in, and then used the Sapoderm soap or the wall mounted Triclosan solution that was instituted in all the bathrooms in the hospital.

They are asked to do that, and we checked on them to see what was going on. I'm very sneaky.

You tell nurses what to do. Then you go and ask the patients if they're doing it, and that's what I ended up doing, going around and doing spot checks on the patients to see if the nurses were actually complying with what we're asking them to do.

It was only a small exercise, because we did it over six months. In the control period, which was the six months in the year before to get rid of any seasonal variation, there was 11,500 patients that we used as a control, and in the trial there were 12,860.

These were patients that were not -- that were in hospital for over 24 hours. So any daily patients were excluded.

We looked at the development of any new hospital acquired or community acquired isolates of MRSA. We looked at their antibody sensitivities. We actually looked at the phage type and the site where the MRSA was first detected.

The results of that were new hospital acquired MRSA in the period reduced statistically to a p value of .00176. For the first time, we were able to show

that the introduction of one variable or the alteration of one variable in the form of Triclosan body washing was able to significantly reduce MRSA carriage and infection within the hospital itself.

When we looked at the sites, although they weren't statistically significant, they are interesting to note, because the wound swab results dropped, and the nasal carriage dropped as well, which is what you would anticipate with MRSA actually being shed a lot through the hospital on skin flakes as well as on staff hands and on the ties that all of us are wearing at the moment.

What we found that was quite interesting, and here my computer went berserk, is the ciprofloxacin sensitivity. Before -- The six months before we started the Triclosan, 8.3 percent of all our MRSA isolates were actually sensitive to ciprofloxacin, and that paralleled with the Australian Group on Antibiotic Resistance, the AGAR group, that says between five and ten percent of all MRSAs in Australia are sensitive to cipro.

During the trial that increased to 17.4

percent. After the trial we continued using the Triclosan because it was so effective. It went up to 22.5 percent for the six months following.

We were able to show that, looking at new isolates, we reduced the MRSA that came through. We found that there was a change in the antibiotic sensitivities for the MRSA. We detected changes in the phage typing that came through as well, particularly in the reduction of one particular phage, which was -- I'll check my notes -- a phage that contained 85/95.

The first site detected, we also found a decrease in wound swabs and in, as I said, nasal carriage.

Where do we go from this further? We have to look at ways that we can see if our findings, particularly in relation to phages and the ciprofloxacin sensitivity, are being able to be proved directly from the use of the Triclosan, but I think we've been able to find, and I'm taking some of the comments that were made earlier -- we tried to find, by using one variable change over a significant number

of patients, that the variable such as a topical antimicrobial wash could effectively reduce the carriage of MRSA within our hospital.

With the evolution of multi-resistant organisms throughout the world, the judicious use of topical antimicrobial agents is something we as a scientific body should look at.

Thank you kindly.

CHAIRMAN BRASS: Thank you. Are there any questions from the panel? Yes, Dr. Larson?

DR. LARSON: We've done a couple of studies like this, and as I mentioned before, always a big confounder has been when there's been a change in infection rates on certain units and hand washing frequency changes.

Do you have any -- Did I miss that? Did you talk about the frequency of hand washing?

DR. MARSHALL: Yes. With the hand washing solutions, it was like walking around with my mouth taped over, chomping at the bit; because people were allowed to do what they had been doing, and my job was to see that there were no changes.

So I couldn't go around and say your hand washing technique is lousy, let's fix it up. I had to just bite my tongue, because that person has been doing it for the last two years, and I'm not going to change that.

I wanted very, very much so to make one variable only.

DR. LARSON: No, but my question is: During the time of the change, did you have any -- I'll give you an example. In the middle of a similar trial we had a VRE outbreak, and we had to tell people to wash their hands more.

So here we are testing a product at the same time as the frequency of hand washing tripled.

DR. MARSHALL: Right. If I was in that situation -- we luckily, so far, haven't had any VRE in the hospital. If that occurred, I would have to terminate it, because that's not a variable, and my aim was to change one variable alone, and I would have had to shorten the period of the trial because of that event.

CHAIRMAN BRASS: Other comments? Thank

you.

The final speaker in the open public hearing is Dr. Syed Sattar.

DR. SATTAR: Good afternoon. Thank you very much for giving me this chance to express my views on the importance of viruses and their elimination from hands. Some other speakers have, in fact, set the stage for me very nicely, making my job somewhat easier in this regard.

I am a professor of microbiology, and I am also Director of a recently created Center for Research and Environmental Microbiology at the Faculty of Medicine, University of Ottawa in Canada.

I would like to give you a very quick overview of what I am to present here, give you my perspective of the situation with regards to infectious diseases in the United States, talk to you a little bit about where viruses fit as disease agents in this picture, talk about the role of hands in the spread of viral infections, show you some data from our studies accumulated over several years about how well certain types of viruses survive on human hands,

and what implications it has in terms of those surviving viruses to be transferred from hands to -- from contaminated hands to clean hands or from contaminated hands to clean surfaces that those hands touch, and then show you some data on the use of hand wash/hand rub products and their potential to eliminate viruses from such contaminated hands, and then conclude a few remarks at the very end. Thank you.

I'd like to point out that I have been conducting research on infection control with particular emphasis on chemical germicides for many years now, and the Center was set up with this research focus in mind. Because of this, I have conducted studies sponsored by many of the companies present here, because over the years we have been given contracts to conduct research.

My visit here is also being sponsored by the industry coalition.

My concern has been, and I have made this remark wherever I have had an occasion to, is to say that the tentative final monograph totally ignores

viruses.

When I raised that question two years ago in an FDA meeting discussing the health care continuum model, I was told that the FDA may consider issuing a separate monograph dealing with viruses; and if that exercise is going to be as slow as the one that we are dealing with now, then I certainly won't be around to see it materialize.

So I think it's an issue that we need to come to grips with, and I think the data that Dr. Guzewich presented reinforces the point that I am going to be making here, or I will reinforce the point that he has made. The next one, please.

With regards to infectious diseases in the United States, the picture is in fact changing, and in some ways not for the better. These are data from the CDC, a publication by Pinner et al. in 1996, which shows that between 1980 and 1992 there has actually been a 58 percent increase in fatalities due to infectious diseases; and if you take away the contribution of HIV as the infectious agent, that increase still amounts to about 22 percent.

Those are, I believe, sobering numbers. As a result of this increase, infectious diseases now rank as the third leading cause of death in the United States. There are -- These are rough estimates, I would imagine, suggest that more than 166,000 fatalities due to infectious diseases, and that, of course, amounts to more than eight percent of the fatalities recorded in the United States in any given year in recent years.

In addition to fatalities, infectious agents also cause more than 740 million clinical cases of disease per year, and such infections account for 25 percent of all visits to physicians, and a very crude estimate is that this has an impact on the economy of the United States in terms of $120 billion per year.

Now these figures do not take into account the impact due to delayed outcomes such as post-polio syndrome and so on, and synergistic effect. There is now some evidence to suggest that relatively mild infectious agents, if they are affecting individuals who have been pre-exposed to certain kinds of

industrial chemical, might in fact suffer much more serious side effects than any one of these two components on its own.

Then we don't have any data, any credible data, on the productivity years of life lost. Thank you. Next one.

What are the viruses that I want to talk to you about? Here is a list. I think it's a pretty complete list of viruses that have a strong potential to spread through contaminated hands: Hepatitis A virus, which causes infectious hepatitis, and it is frequently involved in food borne outbreaks and also outbreaks in childcare centers; rotaviruses, among the major causes of acute gastroenteritis throughout the world and, certainly, United States is no exception.

Every year in the cool and dry period of the year, you see outbreaks of rotaviral gastroenteritis in institutional settings, nursing homes, daycare centers, hospitals, and schools as well.

Chylisi viruses are a somewhat more amorphous group, but among Chylisi viruses the Norwalk

agent certainly is an important cause of acute gastroenteritis, and this spreads in institutional settings as well as related to food borne spread.

Rhinoviruses, which are the major cause of the common cold, now only survive well on human hands, which I will show you some data for, but they also have been shown to spread through contaminated hands. These studies were done -- quite elegant studies -- by Dr. Jack Watney over the past several years to substantiate this particular relationship between contaminated hands and the spread of the common cold caused by rhinoviruses.

Adenoviruses cause eye infections, gastroenteritis and other types of infections, and these are quite a problem in eye clinics where the hands of ophthalmologists have been incriminated as the vehicle for the spread of adenoviruses.

Enteroviruses are an even more amorphous group, but they causes infections such as hemorrhagic conjunctivitis, gastric infection, central nervous system infections, and a variety of other clinical conditions in humans. Next one, please.

As I said, this histogram consists of data that we have generated over many years, and as you can see, rotavirus after its placement on the hands of adult volunteers and when they were sampled 20 minutes after that inoculation, you could detect nearly 60 percent of the infectious virus still being alive.

Similarly figures for rhinoviruses, and these compare extremely well with staphylococcus aureus, which is a virus which is by nature designed to live on human skin. It eventually dies, of course, depending on the type of strain that you're talking about, but the one that survives the best in our hands has been hepatitis A virus.

We have shown that even after four hours of such sampling nearly seven percent of the virus still remains viable, and that is, of course, half a normal person's work day. If they don't wash hands during that period, then they could carry substantial amounts of hepatitis A virus on their hands.

In contrast to this, enveloped viruses -- these are all nonenveloped viruses that I'm talking about. Enveloped viruses such as parainfluenza virus

do not do well on human hands, and there is no evidence that they actually spread through contaminated hands.

So there seems to be some direct evidence or indirect evidence to suggest that those viruses that do better on human hands have a stronger potential to be spread through such contaminated hands.

E. coli, a bacterium, a gram negative bacterium, doesn't do well, and this is also mentioned by Dr. Leyden a few minutes ago. Next one, please.

We have conducted some studies to show what happens when hands interact with other hands and when they interact with environmental surfaces in everyday settings. We have been able to do this through three models.

We had contaminated hands touching clean metal disks. We had metal disks which were clean, which were contaminated touching clean hands, and then one contaminated hand touching a clean hand, just to try and quantitate how much infectious virus can be transferred.

In this case, we worked with a rotavirus which was actually suspended in a ten percent fecal suspension to simulate as closely as possible a natural situation.

As you can see, if the inoculum was allowed to dry for 20 minutes, there was 16 percent to about eight percent transfer, depending on which model you were talking about. This was a ten second contact with a very light pressure, which is only about one kilogram per centimeter square, which is not an unusually high pressure. This is the pressure that you encounter in many, many everyday situations.

I would also like to point out that these experiments were done without any friction during this contact. If you apply friction along with this contact, then you can actually increase the level of transfer by two to threefold. So friction plus contact, even more important in terms of virus transfer.

Next one, please. In terms of interrupting the spread of viral infections in whatever setting that you may want to consider, I'd

like to present to you this general scenario.

You have a virus being released, either in feces or nasal secretions or ocular secretions. If that released virus contaminate hands and if that virus then manages to survive on those hands, you can have direct inoculation of that individual or another individual in the care of this person going directly from those contaminated hands.

Hands can also transfer that virus over to other vehicles, and that other vehicle can eventually also lead to exposure of susceptible individuals in that particular setting. This may result in infection, and cases of infection may result in disease. Not all cases of infection result in a clinical case of disease.

Whether it is an infection or disease, there is shedding of virus from that infected case. So you have that cycle repeating itself again.

If you want to interrupt this, one of the means in terms of the use of germicides is that you bring that germicide in either through decontamination of hands or decontamination of environmental surfaces,

and you can, in fact, interrupt that transmission.

I will show you some data from our own work. Next one, please.

If you look at the case of two viruses that, again, we worked with, hepatitis A virus and polio virus, if you wash experimentally contaminated hands with 70 percent ethanol, there was such a high level of reduction in the level of both of these viruses that one could not show any transfer from such hands to environmental surfaces.

On the other hand, if we used an antibacterial soap with .3 percent Triclosan, there was .6 percent transfer in both of these cases. Unmitigated soap, on the other hand, gave you somewhat higher transfer, and tap water alone with about .5 parts per million free chlorine gave you between 3 and 4 percent transfer.

Next one, please. If you like to look at the relative efficacy of hand wash agents in reducing the contamination, this set of experiments is based on our work with rotaviruses. If you take 70 percent isopropanol or 70 percent ethanol, they are extremely

good in their rotavirus inactivating activity, and more than 99 percent of these viruses could be eliminated within a contact time of about ten seconds, which I believe is much more realistic than 20 seconds.

On the other hand, if you take unmitigated liquid soap, the level of reduction was approximately 76 percent, which in fact wasn't much better compared to tap water. Next one, please.

This is a more recent study that is still under progress. This is why I'm not giving you standard deviations and so on, because we haven't really analyzed the data. I just want you to focus on the trends here.

We have tested an antiseptic gel which contains 60 percent ethanol. There is close to a 3 log reduction in the amount of infectious rhinovirus on the hands of these adult volunteers.

If you take a hand sanitizer which has a 62 percent ethanol, the level of reduction is, in fact, 4 logs or greater. Then if you take a hand rinse which has 78 percent ethanol plus chlorhexidine

gluconate, the level of reduction was just over 2 logs.

With standard hard water containing 200 parts per million of calcium carbonate, the reduction was about 90 percent. The question is: Is this significant between hard water rinse and these other products?

I'd like to submit that, yes, it is significant, because this is a tenfold difference. if you were to do statistical analysis, you probably would find that there is significance.

The other factor that I'd like to emphasize here is that most of these viruses, and this was again alluded to by John Guzewich earlier on, have a very small minimal infective dose. So the higher the level of reduction that you can achieve, the higher is the level of risk reduction and risk management. Next one, please.

This, in fact, should say concluding remarks here. Viruses are important pathogens, and one cannot deny that, especially in daycare centers, hospitals, food handling establishments, and also in

nursing homes.

Many viruses can survive well on human hands. Therefore, human hands can have the potential of being able to access vehicles for such viruses. Many viral infections can be indeed spread through contaminated hands, and hand washing or use of hand rub agents have been shown to be effective against several types of viruses, but we need to do more studies in the particular context.

Such effective agents can also interrupt the transfer of viruses, therefore can interrupt the chain of spread of viral infections. I believe, and I am willing to discuss this point even further, is that in situ virus inactivation is not necessary.

With alcoholic rubs, there is in situ inactivation, because there is no subsequent washing of hands; but if there is a product such as a soap which dislodges your viral contamination and you can wash it off with subsequent rinsing in water and drying or whatever, I believe that the end result is achieved.

So one must not really insist on in situ

inactivation. If you were to do that, you would require much more potent products which, I can guaranty you, would not be user friendly. Therefore, you would, in fact, create a problem of reduced acceptance and compliance.

Testing of surgical scrubs, preoperative skin preps and body washes is not necessary against viruses, simply because viruses are not found as a part of the resident flora of human skin. Therefore, the emphasis has to be on hands, hand washing or hand decontamination agents.

I believe that, if you use the right products with the right degree of compliance, you will, in fact, lead to a reduce risk of spread of infection in daycare centers, in food handling establishments, in nursing homes, and in many hospital situations.

Thank you very much.

CHAIRMAN BRASS: Thank you. Comments for Dr. Sattar from the panel? Thank you very much.

DR. LARSON: Actually, could I just -- Sorry. In your next to last slide you talk about an

antiseptic gel, a hand sanitizer, and a hand rinse.

If I were a consumer or a food handler, I would think those are extremely different products.

DR. SATTAR: Yes.

DR. LARSON: And you know, I'm not sure they are. Could you say why you use those terms?

DR. SATTAR: Yes. Indeed, I am using the terms that were provided to us by the sponsor, and I am also not privy to the entire formulation.

The active ingredients were listed as being either alcohol alone or alcohol and chlorhexidine gluconate, and I believe that the intent of the sponsor is that they are meant for different uses and different settings.

CHAIRMAN BRASS: As we heard today, this discussion has been going on for 25 years. Therefore, this esteemed panel should have no trouble in resolving the issues over the next two hours. That's why they gave us two instead of one.

Perhaps to get us started in our discussion, if I could ask Ms. Lumpkins from the FDA to give us some focus and orientation as to our

objectives.

MS. LUMPKINS: You give me the hard part.

Seems to me that the discussion has been sort of coming from all over everywhere, and the only way that I can see to focus it is to try and go back to the performance attributes that I discussed earlier today and see if we can come to -- well, not even any conclusions, but if we can discuss in the context of broad spectrum, persistence, fast acting, what the committee feels might be appropriate for a demonstration of each one of these traits.

Let's try and stay away from, if we can, particular products or technical discussions on the merits of different types of testings, and just in very general terms.

Then the second question is whether or not these particular attributes have got to be specific for each drug product category. So the same discussion points.

That makes sense to me -- I'm not sure that Dr. Katz agrees -- to start with should they be specific for each product use, and go from there;

because it may make a difference on your discussion of broad spectrum.

In other words, if you decide that one test fits all, it makes a difference to, well, broad spectrum. Do we tailor it to the use of the product or do we not?

CHAIRMAN BRASS: So would you like a discussion of the attributes or the testing first?

MS. LUMPKINS: Basically, for each attribute what do you consider an appropriate demonstration that a product has over a spectrum, but I think probably the better way to approach it is to say should this be product -- intended use specific?

In other words, would the spectrum that we would like to see for a patient prep or skin prep necessarily be the same we want to see for food handlers? I suspect that the answer is going to be no, which is why I thought maybe we might want to get that question out of the way first.

CHAIRMAN BRASS: Okay. Why don't we address that question specifically first then. That has to do with the broad categories of products as

defined in the monograph, as well as the general question that's listed as point 2, should testing requirements be based on intended use and, if so, how.

MS. LUMPKINS: Right, and don't focus in on what particular types of products. If there's any way that you can group them, let you see that there might be some similarities as suggested by some of the speakers today, then that's fine.

CHAIRMAN BRASS: Okay. We'll try starting there. What I'd like to do as a format is go around the table and ask each member of the panel if they have anything to contribute, to make some comments.

If someone from the panel, industry or any of our consultants have a response or an elaboration based on the specific comment made, please feel free to do so.

I would ask those people who are not on the panel to simply move to a microphone. I will try to recognize you. If I don't, wave your hand and, if that fails, then and only then feel free to throw something at me, but don't hit Dr. Koda-Kimble.

Okay. So perhaps, Dr. Larson, you would

like to get us started on the issue of different indications or different intended uses of these products and its impact on the monograph and testing.

DR. LARSON: Actually, I was just hanging out here, because the table is comfortable. I'm not really on the panel.

CHAIRMAN BRASS: You moved back.

DR. LARSON: Thanks for the invitation.

CHAIRMAN BRASS: No, your name is on my list. So you are --

DR. LARSON: Well, it seems to me that if something is broad spectrum, it's broad spectrum. I mean, those two questions aren't mutually exclusive.

Yes, we probably will want different agents for different uses, but I think those characteristics have been defined, and there's not a lot of need to spend a lot of time defining what broad spectrum is.

CHAIRMAN BRASS: What about the differences in issues like persistence, onset?

DR. LARSON: Well, again, either an agent has persistence or it doesn't. The question is when

do we need it? The issue is not what are -- if, in fact, -- I mean, I think those things have been defined. What hasn't been defined is do we -- as Dr. Maki suggested for surgical applications and pre-op skin preps, persistence would be, I would think, at least theoretically and based on clinical evidence that he and others have shown, a good characteristic.

I made the suggestion that there doesn't seem to be any clinical evidence that I know of -- and I may be wrong; please jump up and correct me -- for a value added for persistence for a health care personnel hand wash.

So maybe those are the kinds of issues to discuss.

CHAIRMAN BRASS: In some of your comments and others, you mentioned the appropriateness on an intended use base differentiation between resident and transient organisms. Would you like to add anything to your earlier comments?

DR. LARSON: Not really. I do think it would be a useful discussion to talk about whether the -- we keep -- Seems to me that these food worker --

the food handling requirements, etcetera, are different not for any rational basis, but because they were regulated under a different group before, and they've just come into a new -- and so basically, what we're doing is we're taking two groups and putting them together, and artificially --

There are some differences in need there, but maybe not as many as we might think initially. You either need an antiseptic or not, and if you need one, do you need persistence or not? That's the question, I think.

CHAIRMAN BRASS: Okay. Which you implied in general framework of answer. Thank you.

Dr. Rice?

DR. RICE: I would tend to concur with Dr. Larson's comments. I don't have anything additional to add.

CHAIRMAN BRASS: Thank you. Dr. Melish?

DR. MELISH: Well, I'm still a little confused about attributes and categories. We seem to be talking about both of them. I'm generally in favor of simplifying things.

I would think that there are two categories maybe only that we need to talk about. One is the category about cleansing the hands of workers, and another category of preparing the skin for a surgical procedure.

I do think that the attributes should be different for both of those, because I think they're really quite different.

CHAIRMAN BRASS: Where would you put the consumer and home use in that spectrum?

DR. MELISH: The same as a caregiver and a food worker, I think, because they have the same needs. They want to cleanse their hands for a task, and they probably want it as broad spectrum as possible, because it's the same duty to your family as it is to your patient or your client in a food working situation.

CHAIRMAN BRASS: And you said the attributes would be quite different between those two classifications.

DR. MELISH: Could we talk a little bit about persistence. Given that, generally, the food

worker -- particularly, the caregiver and maybe the food worker hasn't got as much need for persistence, because they should be washing their hands prior to a task, and will probably need to -- to be effective, will need to do it frequently because of the different things that they're doing.

They will contaminate their hands by seeing patients or picking up that chicken, and then they will need to wash their hands again. So they don't need so much persistence, and they probably need broader spectrum, because they have a lot of hazards that they are trying to mitigate; whereas, with the preparing of skin surface for, you know, safe surgery would really have a narrower range of pathogens that need to be treated for but a greater need for persistence.

CHAIRMAN BRASS: Thank you. Dr. Koda-Kimble.

DR. KODA-KIMBLE: I actually was taken by Dr. Larson's suggestion that we look at issues of risk as opposed to personnel. For example, an individual in a nurse or childcare situation where there was an

outbreak of a certain condition or if you had an ill person in the house or if you had somebody who is susceptible to illnesses, might require a higher level -- I don't know what -- or some level of antisepsis and hand transmission than someone, for example, who uses it routinely for general hygiene, for example in the kitchen or in the bathroom or that sort of thing.

I do think the issue of skin prep is slightly different, just because of the resident organisms at the site. I do, though, think that time to kill should probably be the same for all of the products in any risk. It seems like you would want to get kill right away.

Persistence, I think, may not be an issue for health care workers, but I think would be an issue for any other situation that was high risk, because there's no -- It's unlikely that they would be washing their hands 30-50 times a day.

DR. LARSON: I'm not saying it may -- I think, you know, theoretically, it's a good characteristic to have, and I don't want to put us down going in the wrong way. I'm just saying we don't

know, as far as I know.

If anybody here knows of studies that have shown added value to the characteristic of persistence, then I hope they will speak up.

I don't think -- I hate to see us go back and reinvent this entire thing again. I'm just asking if we could maybe simplify somewhere between what the TFM is and what the health care continuum model is. There's got to be some way.

Categories aren't as separate as we think they are. I'm not arguing for only two or three or any number. I don't want to put us down a path like that, but --

DR. KODA-KIMBLE: But I think we could think of many, many situations where an antiseptic would be required, where hand transmission is at issue. I think, if the panel or some group could define what those situations are where it's a health issue or a higher potential health issue, and if we could describe a product that meets -- that is likely to diminish risk of transmission, I think that would be very valuable to the public.

DR. LARSON: Yes. An analogy would be the old isolation systems we used to have that were disease specific, like isolation for staph wound infection or whatever, to this new concept where you have certain precautions for everybody -- okay? -- standard precautions, assuming everybody is infected with something that's potentially dangerous, and then you have levels, depending on the risk category.

So maybe a different way of looking at it, rather than the food service person, the health care worker might be much more helpful and will make more sense intuitively even to the consumer, and by consumer I mean all of us, not just the person in the home, but to all consumers.

CHAIRMAN BRASS: Dr. McKinley-Grant.

DR. McKINLEY-GRANT: I must say, when I first started out with this, it was totally unclear what we were to do, but I feel like we're focusing a little bit more, and I feel like so much work has been done in these different areas about the studies, and we're not even at the point of talking about whether one product is better than the other. I mean, this is

-- We know that they work, and I think we need to use that to our advantage.

I agree with Dr. Larson also in terms of looking at everyone as the same, you know, in terms of the potential for infection or for receiving infection.

The other thing that I am concerned about, though, is the viral coverage. I think we have a structure that maybe we could put antivirals in. I think it's a very -- you know, rather than going all the way back to base one to another monograph to, you know, 20 years later, it seems like we have a structure that maybe we could stick in antivirals here.

CHAIRMAN BRASS: Dr. Blewitt.

DR. BLEWITT: Well, just a couple of points here.

First, I think there's been general agreement, as I have seen it, that the testing criteria, as stated in the TFM, are not adequate to today's needs.

CHAIRMAN BRASS: We'll come back to the

testing.

DR. BLEWITT: Okay. Although I just sort of wanted to comment on that, because it also concerns something else I'm going to say.

I think also that the health care continuum, as I see it anyway -- that it does demonstrate that there are differences in these products, particularly if you look at both ends of the spectrum.

I wouldn't consider a surgical scrub on a par with an antimicrobial hand wash or body wash. So I think that, although you can argue about how these things are classified, still I think there's a recognition of subtle or perhaps important differences in these products.

Having said that, I also get the sense that there are commonalities that exist as well in terms of criteria that you would establish for testing requirements, whether it's time to kill or things like that.

So there may be certain things that are common to all the categories, but there may be very

different criteria for different categories as well.

So I would importantly ask that -- You know, as you recall, the TFM does not include consumer antimicrobials. I think it's important that these be put back into the monograph and that there be agreement that, however they are stated or however they are categorized, they do become a part of the monograph again, because right now they've been left out. Okay?

CHAIRMAN BRASS: Dr. D'Agostino.

DR. D'AGOSTINO: Yes. Could you state again what question I'm supposed to be answering?

CHAIRMAN BRASS: If I knew you were going to ask that, I would have waited until the very end to call on you.

We are addressing the general area of the impact of differentiation of intended use and attributes in classifying and talking about this broad group of agents. Is there value for differentiating them based on use, and how does that link to the attributes each use should have?

DR. D'AGOSTINO: I guess the answer is

there are different uses, as we heard and so forth, and possibly developing tests that are getting into testing procedures that focus on those have some merit to them.

My general feeling is that we've heard this material a few times ourselves. It's not the first time that we've been presented with it, and there's quite a spectrum already. If you start now taking the health care and splitting it up even further, which I think you, obviously, do in reality, but in terms of talking about procedures for testing and talking about giving some guidance to the FDA, I think it gets sort of overwhelming, that you get too particular.

I would argue that maybe we should realize that there are lots of sub-uses and what have you, the daycare, different hospital settings and so forth, but think more of the commonalities in terms of any recommendations we give.

I do want to -- I guess the next question is to talk about the particulars of some of those procedures.

CHAIRMAN BRASS: Dr. Tong.

DR. TONG: I don't have a whole lot more to add to what I've heard. I do want to get into the discussion about the particulars.

I think the point that was mentioned about consumer monographs makes sense, because if we're going to address the attributes by looking at risk characteristics versus the individual use situations, that's going to bring in how we deal with consumer and the information that's going to be conveyed to a patient -- or a consumer, I'm sorry -- you know, dealing with things like viruses.

CHAIRMAN BRASS: We're not going to reimburse you for the cost of that.

DR. TONG: No, but I was curious to see what was out there. As you know, all of us in the OTC business often are amazed at what goes on.

I think, you know, this is going to be something that is worth looking at, and I do agree that I didn't find much discussion in the TFM on the antibacterial -- or antiseptic body washes and hand washes, and actually, I was reassured when Dr. Leyden

made some, I think, very valuable, helpful information to me in terms of what happens to the patient out there, not the individual where decisions are already made about what to buy for the surgical suite or for the unit ward or for the childcare center.

It's the individual who goes to CVS and finds this on the shelf. So I think a lot of work has been done, and I like the idea of -- maybe simplifying isn't the correct word, but the TFM was getting off the drawing board in 1994.

I thought the health care continuum model was an extremely good response to what came off the drawing board, and this is still the process of looking at those, at both points of views, and coming to something that would be useful, but it's reassuring to know that we're really talking about products that do work. There are just differences, and the differences could be applied to the risk application of these products. I think that's where the work is going to be.

CHAIRMAN BRASS: Dr. Gilliam.

DR. GILLIAM: I'd like to echo Dr. Tong's

comments with respect to the consumer. I think there's a lot of confusion out there as to what the words antibacterial on Lever or on Dial or whatever means, and what exactly are they getting for that money that they spend versus a regular hand soap or whatever.

There have been reports, at least in the Tucson newspapers recently by Dr. Gerber who is one of our faculty members, who has done cultures all around the home, toilet seats, etcetera, and then he's used actually diluted bleach solutions and found how much they reduce bacteria in the home and instance of viral infection and everything, too.

So I think there's confusion on the part of consumers as to what exactly antibacterial means. Does that have like a hospital or a medical standard implied in it?

I very much like the idea of going with looking at risk uses of these different products.

CHAIRMAN BRASS: Thank you. Dr. Krenzelok.

DR. KRENZELOK: Thank you. This has been

most interesting. I certainly feel like a fish out of water with my toxicology background, to a certain extent.

So I'd like to turn the table just a little bit so I can use the little bit of that and talk about risk. I agree very much with Dr. Larson in focusing that risk, and I think that we ought to consider at least narrowing these categories and narrowing the focus just a little bit; because it's quite confusing with all these different categories, I think.

Somewhere in our packet of information there was a quote that was attributed at least to Paracelsus. Basically, what it said was the only thing that differentiates a poison from a remedy is the dose.

A lot of these things are ubiquitous in our home environments and hospitals and so on, but especially, as Dr. Tong was saying, being more consumer oriented, these things are in the home. These types of products are really the most common type of thing that little children get into, for

example, as a common exposure agent.

Now in looking at these particular agents, whether it's chlorhexidine or some of the others, they're pretty safe. I think we're pretty confident about that. You don't have to worry about methemoglobinemia from the conversion of the chlorhexidine to the parachloranalin and things of that nature.

We might have to be concerned about the cationics, if these -- and I don't know exactly what products we'll look at, but the cationics, I think, do certainly pose some particular problems.

So I'm a little bit troubled by that, but a comment that was made this morning, I think, perhaps troubled me just a little bit more, and it had to do with the irritation potential.

Throughout the TFM it talks about the products should be nonirritating in each and every one of those categories. I think -- and correct me if I'm wrong, but I think I heard one of the speakers say this morning that they let the marketplace really dictate what's irritating and what isn't.

I think that one of the things that we ought to be is more responsible and more proactive in determining what's irritating up front than what's irritating after it hits the marketplace. I don't think that's a very positive way to approach products like this.

If we want to enhance compliance, we want people to wash their hands for 20 seconds or for ten seconds or 18 times a day, if it's irritating, they're not going to use it. So I think that should be something that we should take on very proactively.

Something else that concerned me just a little bit this morning, looking at sort of our era of evidence based medicine in the nineties, I was a little troubled about what really constitutes an endpoint here.

If we've reduced the bacterial flora by 2 logs, you know, what's the threshold? What's good? What will basically decrease the risk of transmission, as Dr. Koda-Kimble was saying? What is that concentration, and I realize that gets into testing and a variety of issues, but I really feel confused

about that, and I don't think that we ought to be sort of led down the path of thinking, just because it reduces bacteria by 50 percent or by 60 percent, that it reduces risk by that much.

I don't think we can correlate the amount of flora that's left or amount of bacteria that are left with risk reduction.

So those are some things that come to mind that are a little bit troublesome, that I think need to be thought through a bit. Thank you.

CHAIRMAN BRASS: Thank you.

DR. BLEWITT: I just wanted to make one quick comment about one of the statements regarding irritation this morning and what I heard and what I think was intended by it.

I think any company that I've ever known of, including the ones that I've been associated with, will always do some sort of battery of irritation testing for any of its products. Have to, absolutely. But these panels are often of such a size that you really may not know the overall potential for irritation until there is wide scale use of them.

I think that that was really what that comment addressed in terms of the marketplace driving that particular criteria.

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: I agree with Dr. Larson that the number of categories here seems somewhat artificial and based on the market or use rather than the particular characteristics of the products that we're discussing, and so would favor a labelling or approval process that focused on the characteristics of the products and allow the labelling to reflect its efficacy vis a vis this particular characteristic, whether it's onset, persistence, etcetera.

The only other comment I guess I'd make is that, as we begin to talk about testing, it's clear that many of the tests that are in the TFM don't reflect actual use inasmuch as we don't wash our hands for 30 seconds. I tried at lunch. Couldn't do it. Got bored, and I couldn't remember the words --

DR. LARSON: You can do it if you're watching TV.

DR. NEILL; There's a thought. Put TVs on

all the wards.

So I do think some thought needs to be given to revising the tests to reflect actual use, such that the characteristics that we define or that we choose can be tested in a way that will result in an effect when used, which is advertised. You know, my product is persistent as used, and that's what's seen when you buy it and stick it on your shelf at home or in the hospital or use it for whatever you plan to use it for.

CHAIRMAN BRASS: Please, Dr. Gilliam.

DR. GILLIAM: I want to make just a comment, throw out something about hand washing. You know, we're debating ten seconds versus 20 seconds versus 30 seconds. My kind of way of thinking about this is that, while you say that you're supposed to hand wash for 30 seconds, you might only do it for 15. So you're still getting to where you need to go.

Then what if we say, well, you're supposed to hand wash for 15 seconds. Do then people start saying, well, they say 15, and the only -- that means we only have to wash our hands for five seconds, and

that that will be enough?

That's, you know, kind of my concern about that thinking, is that, you know, if we keep lowering the limits, then people are going to say, well, we really don't need to wash our hands that much. So we won't -- we'll get to the point where we're essentially just passing them through the water, and that might be it.

So that's my concern with hand washing there.

CHAIRMAN BRASS: Dr. Larson?

DR. LARSON: I think this is an example of getting mired down, to some extent. Not that it's not important. It is, but there have been studies, as I said, for example, to show that ten seconds is the same as 15. Okay.

The thing is -- and we know that our outcome, our objective, is reduction in infection. We know that, and we're not there totally with evidence for that, and some of these things -- I think this committee is going to have to just decide what is a reasonable expectation to demonstrate that what goes

out in the market is safe and efficacious to the extent that we know, given right now, and then let's just keep, you know, the work coming.

In some ways, it's almost better to get this thing finalized than to go another decade waiting for the clinical trials that wills be the definitive trials. It seems to me that just a reasonable, reachable standard to demonstrate that there is a good product and a bad product, and that the good product meets a certain -- is in a certain category for use.

That would be great, and that's sort of all this group can do right now.

CHAIRMAN BRASS: I personally think that much of the problem we have coming to grips with this is because of the -- and the word continuum in the model proposed by the coalition is appropriate, because there's absolutely a continuum of indications.

You can make it five. You can make it 55. You can make it 55,000, if you try to define the different uses. But at the same token, I think it makes intuitive sense, even in the absence of data, that the characteristics to prep a patient for surgery

are different than what the average American household needs to wash their hands with, and that in the absence of such additional information, it's hard.

If you take the analogy to classical products, no drug antibacterial would be approved simply because it killed bugs. It would require an indication to be used, and whether or not that was meningitis, pneumonia or whatever would make a very large difference in how that drug actually reached the marketplace.

It seems to me, we're at the stage of defining what is ar antimicrobial, what is an antibacterial, and not what the indications for their use are; because, in fact, the data for the indications for the use, which we're going to talk about in the testing, may be very, very different, but in ways we can't fully define yet.

I think the other point that was made, and I think there would be consensus about -- so I just want to reiterate it -- is that linking -- making pathogen synonymous with bacteria has to stop, and that what we're talking about in these agents is the

full spectrum of infectious agents, not just viruses but coming from Harbor, mycology is kind of important. So candidal infections are very important, and as parasitic infections will be in certain select populations.

So I think that, when we talk about spectrum -- and that will be linked to the specific indication as to how important that is, but I think that goes without saying.

So I think, from that framework, we can now begin, if it's okay with the agency, to begin talking about some of the specific testing methodologies and how some of the things we have heard and discussed would interface with that kind of intended use framework.

Dr. Larson, would you be so kind again?

DR. LARSON: You want to talk about specifics?

CHAIRMAN BRASS: Any issues that you feel in the area of testing methodologies, hopefully not focusing on the number of seconds of hand washing but thematically and conceptually that are important to

incorporate into this rulemaking process.

DR. LARSON; Well, let me start with a general comment I made before. That is that the problem with the old TFM from '74 is that there were no controls. There were no standards against which to compare.

Now we solve that problem, but what is the most important clinical organism or -- not even the most important clinically. What if we find out that something is better than Serratia? Okay.

Why do we have to be so prescriptive in some ways? I understand there -- What's the fine line between comparability and flexibility that is needed for some of this testing? I mean, just for starters, where is the test for the waterless products, and how do they merge with those E-1, E-2 things from the food handling stuff, which is a whole different testing thing?

Those somehow, it seems to me, have to be merged.

CHAIRMAN BRASS: If I could just follow up briefly on that flexibility point, because I think

it's very important. I think that, given particularly the expectation for innovation in the marketplace and by industry to preclude an innovative product having a different prescription for use, for example, that might only require three seconds of hand washing or perhaps for a special indication 60 seconds of intensive preparation would be ridiculous to remove the flexibility from a sponsor to develop innovative products with innovative uses.

I know the TFM does say "or as described by the sponsor" in those testing, and I just want to reiterate that. Is that what you were going to say?

MS. LUMPKINS: Well, beyond that, one of the things that I was going to point out is: One of the reasons that we went with such prescriptive protocols in the TFM is we wanted -- Everybody in this room knows that the way you conduct the test impacts on the results that you get.

We were looking for some commonality of procedure so that, when you grab the product from the shelf, you would know it had been tested in a particular way, and that they had all been tested that

way.

So I'm not adverse to flexibility, but there is -- there was that intent.

CHAIRMAN BRASS: Yes, but that's not a philosophically different thing that we usually deal with. If a sponsor wanted to make a claim that a drug was effective against ulcers, you would make some -- there would be some standard ways of doing it, but if an individual sponsor had an innovative way of demonstrating efficacy, the agency historically has worked with sponsors to -- and I realize the scope of this is much larger, but I think the concept that working with more innovative ways of dealing with it is at least as important; because I think what a consumer or the user is going to care about is whether the claim is legitimate, not whether the claim was verified in exactly the same way as the product on the next shelf.

DR. LARSON: I mean, we can start with the easy things, like the new tools. Everybody, I think, is pretty much in agreement there's an issue there. Another easy thing is that, for the application, let's

say, whatever you end up calling the health care personnel hand wash application, i.e., an antiseptic use in a high risk situation, that it should be closer to real life use like maybe 15 seconds or whatever.

Let me just ask, what if a manufacturer wanted to make the claim that their product does in five seconds of contact time what the other products do in 30 seconds? How could they do that? They couldn't get -- It couldn't happen.

It would be a great -- I mean, talk about risk/benefit and cost/benefit ratio. If we could find something that would work in five seconds instead of 30 -- There have been studies published that show that, if people actually washed their hands as often as CDC says they're supposed to, they wouldn't have time for any patient care, and they wouldn't have any hands left.

So anything we can do to reduce the time and the numbers of applications, the better. Yet there's no way for a good company to make a claim outside of the monograph claim. So that means in 30 seconds it works.

CHAIRMAN BRASS: Dr. Katz?

DR. KATZ: Well, there actually are other ways outside of the monograph to make claims.

DR. LARSON: Maybe that's in the NDA process.

DR. KATZ: That would be through the NDA process. So that, looking at the monograph, what you're trying to do is to try to make sort of a level playing field in the sense that this is a standard that everyone should be able to meet -- to be able to make to get the claims that the monograph would set forward.

For an NDA that would be the time to make some innovative claims which that particular product may be the only one that could do or NDA deviations to the monograph and things along those lines.

So there are other options within the regulatory framework of the agency to allow for that.

DR. LARSON: Sure. It just seems to me that there may be things that are now under the OTC that could make other claims, but -- well, anyway, your point is well taken.

If nothing else, then we should have it not 30 seconds then for -- We should have it 15, because no use being able -- I agree with the level playing field, but nobody is going to use it that way in real life.

DR. KATZ: That's actually why we're bringing some of this back up, because as you've even heard from this morning with the discussion is that, when the original 1974 document itself didn't allow -- it was too vague. The 1994 document may be too specific in certain areas so that the standards are such they can't be met.

DR. LARSON: Now the next question is -- Let's say that, as two people have suggested, the consumer products be added again to the TFM. Then if they're going to be used in a different way -- One of the problems now is do they have to pass the rigid health care personnel hand wash protocols, and that doesn't seem reasonable.

CHAIRMAN BRASS: Thank you. Dr. Rice?

DR. RICE: I think I have maybe just a bit more to add. I tend to concur, we need to, if I

understand what I'm hearing, establish and adhere to some minimum standards for compliance criteria, but relative to the prior discussion in terms of risk categories, I think there needs to be flexibility in terms of the monograph and standards so that we can address new and emerging pathogens as well as consumer and population and perhaps new environmental challenges, so that we're able to entertain more innovative and newer claims.

That's what I would like to add to the conversation, but I would tend to concur with the prior comments.

CHAIRMAN BRASS: Thank you. Dr. Melish.

DR. MELISH: I have no more to add at this point.

CHAIRMAN BRASS: Thank you. Dr. Koda-Kimble?

DR. KODA-KIMBLE: I'm going to forget which organization it was, but it's AT -- the testing group? ASTM? Okay.

I don't know about this group, but if it truly is a peer review group that consistently and

over time evaluates testing methodology, I wonder if we could adopt some language that refers back to a standardized procedure that is accepted by the industry as a way of evaluating whatever it is we're going to evaluate, time to kill, persistence, antimicrobial activity, spectrum of antimicrobial activity.

One of the things I did notice in the comments was that there was deviation from those standards and that, in fact, the technology had changed over time, and it probably still will. So it ought to be a living document, something that reflects current reality, as we learn more information.

CHAIRMAN BRASS: Dr. McKinley-Grant?

DR. McKINLEY-GRANT: Okay. I basically agree with all the comments. I just wanted to add that -- and to stress that I think any studies that are done should be actual use studies of, you know, hospital patients, of food handlers, of food workers, of daycare, to try to really get actual use.

The other thing is dermatologists. If you could include diseased skin and normal skin in some of

the studies, I think that would answer -- help to answer some of the questions about irritation and who can actually use some of the products.

CHAIRMAN BRASS: Dr. Blewitt.

DR. BLEWITT: Again, I think -- and I think Dr. Larson just sort of emphasized the fact that testing criteria should be specific to the specific product category in citing the difference between health care hand washes and consumer hand washes.

I, frankly, think that this particular subjects gets to the point where the details go beyond the scope of this group to handle. My suggestion would be that there be some sort of continuing dialogue to hammer out the details of the testing requirements with the appropriate interested parties, industry, FDA, whether it involves ASTM or whoever, that that is the way that it is eventually resolved.

CHAIRMAN BRASS: Let me, since you raised it, ask you, but asking the panel, a rhetorical question in response to that. I agree that it's probably inappropriate for us to pick a kill level today --

DR. BLEWITT: Right. How many seconds.

CHAIRMAN BRASS: -- to be on page 342 of the monograph. However, I would ask you, what information would you like available to set an appropriate kill level for efficacy for a consumer product?

So in other words, if -- We're talking about claims being made. If somebody was to claim -- don't worry about what it met, but if they wanted to say they could claim that their consumer product killed bacteria on the skin.

DR. BLEWITT: All right.

CHAIRMAN BRASS: If it killed one bacteria, would that be enough for the claim? How would you suggest that information be processed to allow a decision to be made without having access to the --

DR. BLEWITT: Well, you would have to look at the database and the sufficiency of the database in terms of how much direction you get from that, and that would include both published literature and any data contained within companies that they're willing

to share.

Then -- One of the ways I sort of look at this is statistical versus clinical significance. What is meaningful? I think that probably those who are best educated in that process, probably a combination of people who are basic scientists and clinicians, can try to hammer something like that out.

Does that answer your question?

CHAIRMAN BRASS: Again, it wasn't a question just for you. It was a way to try to help add some focus here.

Dr. D'Agoscino?

DR. D'AGOSTINO: I guess I always feel like I'm missing the discussion. I mean, I'm not convinced that we really have a sense of endpoints, for example. I mean, are all the in vitro, in vivo -- that's what I thought that we were going to be asked. Is this whole plethora of in vitro and in vivo tests -- is that really sensible, this long list of organisms?

CHAIRMAN BRASS: Feel free to answer that question.

DR. D'AGOSTINO: I'm asking him. You know, is that sensible? I thought that's what we were going to sort of grapple with. Is this strategy the right strategy? I'm not saying it isn't the right strategy. I just don't know if I've heard enough presentations today and I've read enough to be able to answer that question.

Some of the comments that you were just making -- I mean, it's another body of scientists and experts that would have to help us. I do have very strong opinions about the clinical trials.

I mean, I spend a lot of my life looking at cardiac problems and cancer problems and so forth, and they have no problem putting clinical trials together. Here it's kind of hard to be told that hand washing is so overwhelming that we can't put a clinical trial together. I mean, I --

DR. LARSON: No. I don't -- I think the problem is that, with surgical site prep, you can. With other things, you can. You probably can with hand washing. Brad Demeling got a good start on it, and there are some people who are doing it, but it is

a little bit harder to control all the confounding variables. It's a complicated study. I agree.

DR. D'AGOSTINO: You know --

DR. LARSON: All I'm saying is this committee shouldn't wait for a definitive clinical trial on every application of hand washing with the outcome being infections, because, you know, that will be here another 40 years for every --

DR. D'AGOSTINO: Well, you know, maybe 20 years ago somebody said that question would have something going now and so forth. I think we shouldn't wait forever also, but I don't think that we should just say, because it's going to take a while, that we shouldn't raise the discussion and then ten years from now somebody else raises the discussion. They say, well, you know, it's going to take a while.

I think the discussion should be raised now, and certainly, I think that we should make recommendations or at least get my voice into it. I think clinical trials are definitely essential and, knowing this, I think we need to know what the endpoints are, and we need to design clinical trials

according to those endpoints.

I do think I'd like to hear some more about these in vitro, in vivo tests and just how useful they are. How do they add? How do they substitute for in-use? I mean, are we really saying that, if you do enough of these, you don't need to do in-use or actual use studies, intended use?

I haven't heard that discussion. I really would like to hear that discussion. I don't think that there are substitutes for them.

CHAIRMAN BRASS: Dr. Tong -- or Dr. Blewitt, did you want to add?

DR. BLEWITT: I was just going to comment -- respond to that comment, which I think certainly has a great deal of merit.

One of the ways I look at this, as I look at this health care continuum model, is that -- and look at the population impact as you go from pre-op skin preps up to antimicrobial body wash, the population impact becomes greater and greater, and I think the way I look at it, the greater the population impact, the more difficult it is to do any kind of

controlled clinical trials.

It's perhaps much easier in a hospital setting than when you try to look at the impact of hand washing on the general population. How do you design any kind of trial that would define those performance characteristics?

So I think, as you get out into larger populations, it becomes much more onerous.

CHAIRMAN BRASS: Dr. Tong?

DR. TONG: I don't have anything to add.

CHAIRMAN BRASS: Dr. Gilliam?

DR. GILLIAM: Nothing further.

CHAIRMAN BRASS: Dr. Krenzelok?

DR. KRENZELOK: One final comment. I heard the term broad spectrum bandied around quite a bit this morning, and one of the speakers this morning, I thought, sort of put some focus on that and basically said that we ought to be performing testing based upon the organisms that you're most likely to encounter, rather than a potpourri of organisms that are just there for the sake of testing.

As I looked at the proposed rules, there

are 20 different organisms, including candida, and perhaps a group with the specific expertise of saying, okay, these are the 14 organisms or the five organisms we should use should be -- this should be referred to them to get some better guidance and provide better direction along those lines.

CHAIRMAN BRASS: I think that's right. I think this goes back to the indication specificity. I mean, to have an indication for daycare center workers that doesn't include viruses doesn't make any sense.

DR. KRENZELOK: Exactly. I agree entirely with that.

CHAIRMAN BRASS: Dr. Neill?

DR. NEILL: Just a few comments, specifically about the recommended revisions in the testing that came from the CTFA. I don't remember what the acronym stands for, but from industry.

A couple of the specific alterations to the tests raised questions in my mind, to begin with. In the preoperative skin preparation category, one of the tests for establishment of the activity of the

product and its ability to show a log decrease suggests that, if you begin with the FDA starts with on the abdomen and groin, there's not enough. So let's put some more bacteria there, and then we'll be able to show a reduction.

That troubles me a bit, and specifically on page 29, footnote 2 to their table, they suggest this, also on page 26 earlier in the body of their text. I guess, because adding bacteria to the skin is going to -- as part of the testing process.

What I've heard today suggests to me that I would be able to show a reduction in that anyway. Put bacteria on the skin. It's going to go away. So I think that this more speaks to the question of whether or not we have any adequate handle on log reductions, to begin with, and is this a reasonable test.

I interpret this suggestion from the consortium more as an effort to come up with something, and I think maybe it was just unreasonable to have something, to begin with.

Second, a couple of people have raised

issues about the consumer use for these things, and there's a comment in the consortium information that I received on page 60, which suggests that they've had difficulty providing the FDA with data regarding the efficacy of their consumer products, because they won't share their data with one another by virtue of combining -- to form some joint set of recommendations.

I'm not sure that that's going to change, regardless of what we say. So I'll just throw that out there. If we decide there are some tests that we want the FDA to apply for claims related to product use in the consumer arena, we may have to do that without data from products that are already there.

Then lastly, just not related specifically to the question of tests and testing, if the process that we're undergoing now is to advise the FDA regarding claims related to the labelling of some of these products, then given that we're dealing with antimicrobials to be used in a variety of settings, the questions that run through my mind are: if there are some very nonspecific claims that are made or, for

that matter, very specific claims -- this will reduce bacterial colony counts -- I guess I would urge that the tests be specifically related to the claim, such that when we begin to see claims made to the hospital formulary committee in deciding what to stock in its operatory, this reduces the rate of post-operative wound infections in hip surgery, that we have some reason to be able to judge that claim.

I think that the Chair has already made that point by saying that we could be here forever and never define all of those, and perhaps that speaks to the need for flexibility. However, given the criteria that are in the TFM in terms of persistence, onset of action, which may or may not have relevance to clinical efficacy in the specific conditions that we think these products are going to be used for, food borne illness and rates of attacks and such, with relation to those specific characteristics it seems like there are some criteria. They're there.

The main objection I heard this morning was that none of the products can meet some of them. Gee, you know, if they're not related to clinical

activity or clinical efficacy anyway, I don't have any problem with changing them, because they may be meaningless. But if the point is to have some test that serves as a surrogate, then choose one.

I'm not in the business of excluding products from the market. On the other hand, it sounds like we are in the business of making sure that the claims that are made bear some relation to reality and need to be fairly specific.

CHAIRMAN BRASS: Thank you. I -- Yes? Please identify yourself.

DR. RESH: I'm Carol Resh from Unilever. I've worked with the coalition now for four years, since we started, and I just wanted to comment, really, on two of the things that you've said.

One was about the patient pre-op procedure and adding bacteria. We didn't actually suggest you add bacteria. The clinical procedure as put forth in '94 suggested that you have numbers that just aren't found, and I think Gale Mulberry is here from Hilltop, and he can tell you, you can't find people that have numbers that high.

So we either said you included it to increase the natural flora by occlusion, which I think Jim showed you earlier will increase the numbers; and we weren't suggesting that you really wanted to add bacteria. It's just that, in order to get the number up there so you can get it, you have to do something, because that number just doesn't exist. Gale can speak to that.

CHAIRMAN BRASS: Again, please identify yourself.

MR. MULBERRY: Gale Mulberry with Hilltop Research, testing laboratory.

The pre-op skin prep -- we've found difficulty particularly in -- This is not on -- predominantly on the abdominal sites finding counts that are at the level specified in the monograph.

Maybe about 20 percent or maybe only 15 percent of the subjects that we looked at on the baseline counts have organisms in that level. So that means, to find a panel of 30 subjects, we would have to screen two, three, 400 people.

It seems unrealistic, because it's not

reflective of what's normally in that area.

DR. NEILL: I guess, as I read that -- not to interrupt, but to do exactly that, interrupt -- another way to interpret that or another way to make a different recommendation could have been lower the initial colony counts that we find to something that we actually see in real life, but have a similar log reduction, which I expect would be a more difficult standard to meet, and maybe impossible like some of the others that we have already seen may be impossible to meet.

MR. MULBERRY: For the abdominal site, it doesn't seem reasonable to raise the population to the level just to meet the log reduction. It seems like we should be looking at a different criteria, a different log reduction.

DR. LARSON: Could I just add -- Gale and a number of us, and I was there as a, I guess, researcher/clinician -- Years ago there was an FDA group that was convened to talk about the testing standards for pre-op skin preps, and I don't know whatever happened. But all of us were saying the

standards are unrealistic and, in order for industry to respond with a test that will meet those standards, they have to create other artificial things like, you know, occlusion to grow up enough bacteria or to screen hundreds of people.

So the problem is getting the standards so that they're doable and relevant. That was at least -- I think it was close to ten years ago. Nothing's happened. So I'm expressing my frustration, because we have been consulting on this, and now, you know -- I agree that we need to go back and use experts or whatever, but we've been, you know, trying to get these things changed.

We've been trying to define relevant clinical outcomes, both endpoints and appropriate surrogate, you know, measures that have sufficient sensitivity and specificity, because you always have to, you know, kind of dance with that one a little bit.

So I don't want us to end up at the end of the day where we are at the end of every one of these meetings I've been to.

CHAIRMAN BRASS: We agree. Dr. Tong?

DR. TONG: I just wanted to add to Dr. Larson's comment about realistic standards, and I'm sitting here thinking about food handlers and feeling that we hold the performance expectations of food handlers, products used by food handlers fairly high, and it's very rigorous, because there's a number of other things that go along with the use of antiseptic washes -- hand washes before food preparation.

I'm extending that to consumers. We talk about, well, you know, it's just on the risk and leave the different categories out, and would it be realistic to apply those same standards and say, you know, this is a product for consumers.

We know that in poison centers we don't get outbreaks of food borne illnesses in public places as often as we get the home situation. I mean, that far outnumbers probably nine to one in terms of, you know, how frequent.

I don't have an answer to this, but I'm just thinking as the discussions go on at the agency level and in industry, one of the things that I think

we'll have to deal with is realistic standards. I'm just thinking about the food handling issue, you know, and how that's going to be handled in a consumer frame and how that's going to be addressed.

CHAIRMAN BRASS: Yes.

MS. RESH: Carol Resh, and I'll just finish my other point before we get too far. When we started -- The document you saw was something we wrote, I guess, January of '95 -- '96. Subsequent to that -- '95? '95, time flies.

Subsequent to that we did submit to the agency blinded company data. Yes, we do have a problem sharing our data among such divergent companies. We have recognized we're in all of these categories. Some of us are more willing to share our data than others.

So we blinded it, and we have now submitted another 16 volumes or something to Debbie and to the docket that has a lot of the -- a tremendous amount of the in vitro data and the in vivo data.

We went back. We pulled all the published

literature we could find, put it in the same format. That's one of the things we had, is everybody sends their data their special way. So we put it all in the same format. So we have submitted data. There is plenty of data in the docket.

I think we just need to move on. If we do need to generate data, we need to know from the agency what we should do, because at this point we don't want to be generating data that they're going to say, well, you didn't write it the way we want it. We need to know specifically what they're looking to.

DR. HAAS: Chuck Haas. I want to tie together two things that I thought I just heard. First of all, discussion on log reduction -- I understand why that originates, coming from a disinfection background, but Paracelsus was mentioned earlier.

The dose does make a poison for microorganisms as well as for chemicals, and in all the dose response modeling we've done, we have not found any evidence for threshold for any organisms.

I would submit to you then that it may

very well be the endpoint microorganism concentration rather than the logs reduction taken to get there that's indicative of the ultimate risk.

One possible alternative that might be considered is to focus attention not simply on log reduction but on ultimate endpoint count.

CHAIRMAN BRASS: Thank you. Please?

MS. BRECK: I'm Mary Breck, and I'm a consultant. I think probably with a few others in the room, I have a record of being involved with this. I was the Executive Secretary for the original panel.

I wanted to answer Dr. Larson's question about where we are with the alcohol product and a test method for that. ASTM -- I hope we are in the last ballot round with a test method based on Dr. Rotter's hand rub and also on the CEN, which is the European standard for hand rub.

So there will be a published test method and, as with all these test methods, there are good and bad points about that procedure.

I also wanted to try, I think, to say something about the nonirritating, which I think we

originally did put in the first publication of the panel's report.

We were looking at that word, nonirritating -- If you all remember, this is an ingredient review, and the intention was to focus the industry and whoever was preparing a product from the monograph that the formulation should be made so that it was nonirritating or an attempt should be made.

I think we all recognize that with antimicrobial chemicals we are dealing with somewhat irritating products and, as Dr. Larson pointed out, really, no matter what you wash with, if you wash enough times a day, you're going to have some irritation to the skin and, certainly, weather conditions and relative humidity make quite a difference in what the irritation results are.

CHAIRMAN BRASS: Thank you. Dr. Koda-Kimble?

DR. KODA-KIMBLE: I'm feeling like we're making it complicated again. One of the things that I feel is complicating is that, when we begin to again think of the spectrum of use of these agents from

childcare, when you think about antiviral effects, to food handling and all of that, I wonder if it is possible to indicate a single standard for antiseptic use in a high risk situation by taking the most -- not everything, but the most common organisms that are likely to be at risk.

If somebody wanted to make claims beyond the usual standard -- because I'm even remembering Dr. larson's presentation. A nurse is not a nurse is not a nurse. It depends upon where they're practicing in the hospital, which patients they're working with, what organisms they're in contact with.

For the public, I think all of us -- and the public are more highly sensitized to the possibility of transmission of infection with improper hygienic techniques and, if the panel could do one thing, which is to say there are products on the market that would be useful, potentially useful, in decreasing transmission of infection, if they are used in the following way, and particularly in the following situations.

I think that could be very useful. By,

you know, saying in this situation you would do this, in that situation you would do that, I think it just makes it ever more confusing.

Now I don't know whether that's being too simple, whether that's impossible, but I would plead for something simpler than more complicated in this situation.

CHAIRMAN BRASS: Dr. Neill, did you have another comment?

DR. LARSON: Dr. Brass.

CHAIRMAN BRASS: Yes, Dr. Larson?

DR. LARSON: One other way that might help us as we grapple with this, because we keep going between what's a sort of standard level or a minimum level of safety and efficacy and what's clinical relevance and what's, you know, the outcome of infections, is to really take -- and it might be possible to even tackle it in two steps.

One is what does the product need to demonstrate an acceptable level of safety and efficacy, and the claim is this demonstrates in a standard way a level of safety and efficacy.

Then the next level even of label claim, for example, might be what is the evidence that this has anything to do with infection.

I do think that we've got enough evidence that there clearly is a dose response and that the fewer germs you have, the less likely you are to have an infection. I mean, that's the germ theory again, but --

CHAIRMAN BRASS: I also plead with Lister, too.

DR. LARSON: Yeah. But maybe we should just tackle those in two separate things. First of all, what would be a way to say this product meets the minimum acceptable standard as an antiseptic or whatever we call it.

Then the next is what standard needs to be met to say that there is actual clinical relevance --

CHAIRMAN BRASS: An indication?

DR. LARSON: Yes, because whether or not, for me personally, there's clinical evidence of reduction of infection, I want to know, first line, is this product efficacious in a certain way, i.e., does

it reduce the numbers of counts, etcetera, and is it safe to use. That's necessary.

Then the next step would be what's the impact. The labelling might be in two levels. So some products might have both claims. Some might have one, but it seems like that would be another way to simplify it for us as we address it, too; because we can't -- Yeah, there are two different related and important issues.

One other comment about flexibility. I'm the Chair of a hospital infections control practices advisory committee, HICPAC, for CDC. We struggle with the same thing.

When we promulgate a guideline and it gets in hard copy in the Federal Register and in journals and so forth, and then a new study comes out and something has totally changed in terms of occupational health or surgical site infection or whatever, what do we do?

The guideline is out there. People are following it. What we've decided to do from now on is to say that this is a guideline effective X date, and

updates will be on the Web X number of times a year.

We know we still have to go through the approval -- the usual government approval processes for changes, but that allows us to have a hard copy with a caveat that this isn't the end and so forth.

Until we can use these new modern methods of keeping things updated, we're going to have trouble with these. They're always going to be tentative. So let's just say they're tentative, effective X date, with updates coming once a year or whatever.

CHAIRMAN BRASS: I think, certainly, as I have thought about it from our previous discussions, as Dr. D'Agostino appropriately points out and as you have as well, Dr. Larson, I've actually come to the construct you just indicated, that there are two different things in my mind.

Is this an antiseptic agent, and does it have an indication for use? The categorization is an attempt to begin to define those indications, but it is not clear how that relationship between the indication and that baseline assessment is linked.

I think in general -- Coming back to Dr.

D'Agostino's point, I think that -- and paradoxically, many of these high risk situations -- the event rates are high enough that there's no question a clinical trial can and should be done, that there is no need to initially assume a surrogate, whether it be in vitro or in vivo, for some of those indications.

Again, I don't know how far down the continuum you want to go to reach that in your initial assessment, but I think, unambiguously, it is so; and those same studies can then yield validated surrogates as opposed to unvalidated surrogates.

Right now, again, I think part of the issue with looking at the data that was presented this morning of "accepted agents not meeting the standard," as was pointed out, there's two explanations for that. Accepted agent isn't really an acceptable agent for that indication or standards aren't right.

I think the use of appropriate positive comparators rather than arbitrary levels, with appropriate statistical power for studies using positive comparators as opposed to placebo control may be a way around an arbitrary endpoint that's a

surrogate until validated surrogates can be identified.

In general, when one considers the use of a surrogate endpoint rather than a definitive endpoint, the risk/benefit of the outcome matters a lot, and when both the benefit is low and the risk is low, then your willingness to accept a surrogate goes up. That may be where you are for the consumer kinds of products, but again it seems to me, listening to the discussion, rather than pretending there is certainty where there is none that simply allowing the flexibility and, in my sense, a positive comparator for what would generally be accepted as a known antiseptic agent and a non-difference or better than test.

I'll let my statistical colleague comment on the problems of using positive comparators as opposed to fixed endpoints or placebo controls, but I think that might be a formulation to get you out of this quandary and this box you've built yourself into.

DR. LARSON: The irony is that there are more data demonstrating the effectiveness of hand

hygiene, both with plain soap and some value -- there are data about some value added in certain risk areas for antiseptic products than there are for many, many other things that we -- you know --

CHAIRMAN BRASS: Yes. I think that's really important, because -- and I meant to mention this earlier. I think it's really dangerous to allow anecdotal statements substitute for existing high quality data or potentially high quality data, that no matter how well characterized the anecdote, it is still subject to a number of inputs and uncertainties that allow it to be used as a basis for decision making, to be no matter than the unvalidated surrogate, in my opinion.

Dr. D'Agostino.

DR. D'AGOSTINO: Yes. You had just stated very much what I was trying to get at in the questions I was raising. I don't know how we sort of interfere with the monograph process, and I think there's a lot of shuddering going on in the audience that what are you telling us to do; but I mean, I think that I have not been overwhelmed by the fact that the existing

criteria is too stringent, not because I don't believe you.

I mean, I think that you -- I presume you're telling me the truth. I just don't have enough data to sort that out. So I'd say, well, lower it if you like, but lower it to what? I don't have the faintest idea why it came up to what it is now in the discussion.

You know, I've been reading this material, and I've been reading it for only three or four years as opposed to 25 years, but I still don't get it, and I don't have access to the particular data that companies are submitting. So I'm deficient on that, but certainly, the stuff that we've been seeing. So I don't know how to move it up and down. But even more, I don't know why -- I don't find it compelling on why this plethora of tests are given, and I keep running to -- My mind keeps saying, well, why don't you do the clinical trials.

I agree 100 percent that it should be a positive control. You have to be careful when you go down to population levels and so forth, but some of

these higher levels -- I mean, I don't know -- As I say, I don't know what interference we're going to get with the monograph process, but I think very much that those should be the types of things that we say at the end of the day here.

As far as the positive control trials, there are a lot of difficulties with positive control trials, but we're well aware of them. And I'm sure a lot of these products that are available, in fact, are useful as a positive control trial.

As these trials are run, we'll learn about them and how they start stacking up and so forth. I think, you know, I'm not so overwhelmingly concerned that the interpretation of positive control trial is going to be anymore difficult here and it's going to foul up the whole situation.

I think that it's going to actually work out a lot easier than in many other fields where positive controls start introducing lots of side effects that you have to really worry about. We don't seem to have that here. So I think these are going to actually be fairly smooth trials, but I do think they

are fouling up the process. But I do really feel compelled to make my recommendations in that direction and --

DR. LARSON: Okay, I agree. So let's take that another step. I mean, seriously, let's think about how you would set up a trial. Let's say that you do it in the classic way so that you randomize. You have two comparable groups in a hospital, and you randomize them to one soap versus the other.

Then -- I am just foreseeing a problem here that I think we should anticipate. Let's say that there is a result which is the result of a rigorous enough clinical -- randomized clinical trial that, whether the results are positive or negative, you can believe them.

The next step is, oh, well, that was in a bone marrow transplant unit with X product. That doesn't say anything about everything else on the market. Oh, that was with an alcohol; that doesn't say anything about CHG. Oh, that was with Triclosan; that doesn't say anything about pediatric people using.

So my concern is --

DR. D'AGOSTINO: I guess I'm overwhelmed with that discussion, but I guess I feel so much more comfortable hearing it happen to bone problems than I am that it happened in a test tube.

I mean, you know, this is what I'm grappling with, that I would be much more comfortable with it happening in a couple of different settings than in no in-use setting, no actual use setting; and I think that that's part of the question.

You have to ask when are we willing to extrapolate? When are we willing to generalize? I think that's part of what we have to do.

DR. LARSON: Right. But what I'm saying is I think that still doesn't preclude a two-step process, one where we have products that meet a certain standard and another where we look at clinical relevance.

DR. D'AGOSTINO: Yes. I'm sorry, but I never was implying the removal of what that was being said. I was going on to these other discussions about the actual clinical testing.

CHAIRMAN BRASS: And I was also suggesting that the positive control could be the standard in vitro testing, too, rather than the arbitrary standard.

I think the issue you raise also gets back to interpretability. When you start doing the clinical test as part of the standard, what formulation changes mean.

DR. LARSON: Frankly, I think that's as much a --

CHAIRMAN BRASS: And that's where we go outside the monograph, and now I'll recognize Dr. Katz.

DR. KATZ: And actually, that's sort of the key into sort of where I wanted to be, as I'm listening to this discussion. I just wanted to remind everyone what we are talking about is really the monograph process, that this is an ingredient base process. We're not talking about specific drug or specific drug product, that this is a broader spectrum, ingredient based review.

So that, if one decides that we would need

clinical trials for what's being discussed here, that would mean we're talking again final formulations, and each final formulation would need a clinical trial.

DR. LARSON: That's the problem.

DR. KATZ: And that's basically why I wanted to sort of bring us back, because a lot of what I'm hearing is a very interesting discussion, and actually I didn't want to stop it. But I wanted to make sure that everybody knows what realm they're going toward, to see if that's really where they want to be, because that may not really answer the questions that we need to have answered for an ingredient based drug review, which is where the monograph comes from, as opposed to a specific drug based trial.

CHAIRMAN BRASS: But is it clear -- Again, is it clear that formulation doesn't matter, for example, for characteristics like persistence in a clinical product, that doesn't formulation matter?

DR. KATZ: Formulation does matter, and actually, it's part of the issues that we're also trying to find, is in which kinds of formulations does

it matter. Which ones do you need final formulation testing, and what kind of final formulation testing do you need.

That's where it kind of brings us back to we all started from, which is that are surrogates adequate for final formulation testing or do you really need clinical trials to do final formulation testing, which is kind of again going round about to where we started from earlier.

DR. D'AGOSTINO: I'm still -- I'm not sure I -- I've been with the OTC review for about 25 years in different capacities of consulting and so forth. So this is what I meant when I was saying how it's going to impact on the monograph process.

I just don't understand the problem you raised as somehow or other saying, okay, then great, let's get rid of clinical trials. I mean, it leaves me even worse that, you know, I --

DR. KATZ: I never said that. What I basically said is that when you're thinking about what you're going ahead to recommend, remember that, being that this is an ingredient based review as opposed to

a specific drug, whatever you propose is going to have to go through the whole spectrum.

So if what the committee comes down and says now is that clinical testing is needed, well, that's fine. That may be something that we'll address, but I just want to make sure everybody understands what process they're going through.

We're not talking the NDA process. We're talking a monograph.

CHAIRMAN BRASS: Yes. And I think Dr. D'Agostino understands that. I know I understand that, and I think what we're trying to convey is that in going from the idealized even clinical trial to developing a monograph based on surrogates, the dotted line at least has to be visible in a somewhat linear way and not a curlicue with huge gaps in it.

I think that's what we're seeing going from what we have now to the monograph in how those surrogates have been formulated.

Other comments from the panel? Are there from the agency's perspective in our free floating angst that we have not addressed for you yet?

Dr. D'Agostino?

DR. D'AGOSTINO: Can I ask what would be -- not from the agency, but from maybe Dr. Larson -- What would be, for example, a nice outcome of this meeting to recommendations for the FDA? I mean, I hear the two-tiered bit, and I'm 100 percent behind it.

I've expressed my concern about the lack of clinical trials. There are settings with clinical trials I use and so forth, and those are sometimes reasonable, sometimes not. You've given the experience you've had, for example, for 25 years or what have you.

What would be, you think, a reasonable set of statements to make to the FDA?

DR. LARSON: Well, actually, we probably said some actually useful things today, and --

CHAIRMAN BRASS: Even if by accident.

DR. LARSON: I think, if we agree that we would like to see as much as possible the test set up in a way that is clinically meaningful, that's something that would be helpful.

If we agreed that there could be the potential for a two-tiered idea so that the claim has nothing to do with infection unless there are clinical trials, but that we could still have a standard that got decided on without having this be -- It seems like this is what always holds us up from moving it forward.

So if we could be real clear in that, and then if we could find a way to allow for fairly expeditious modifications to the monograph in real time, i.e., less than a decade between -- in other words, figure out a way, as new information comes along, to make modifications. Those would be three great steps forward.

I think that the current one is a vast improvement over the first one, and we always like to be hard on the agency. I think it's an improvement. I think there is openness, but there seems to be a level of inability to just decide to go ahead and set up some standards that are reasonable.

CHAIRMAN BRASS: I would add to kind of this compiling list of things that there seem to be

emerging consensus about the need for flexibility and not having the monograph constructed in a way that prevents innovative ways of demonstrating the same objective by the industry.

Yes, Dr. Leyden?

DR. LEYDEN; Jim Leyden, University of Pennsylvania.

Just to follow up what Elaine was saying and somewhat of what I said earlier this morning is that we do have 25 years of experience. We have had proposals and improved proposals, and I think the major thrust of this morning was that some of the proposals now have technical issues that, as Elaine said, could be easily handled.

Now many of you have expressed the appropriate point of view that whatever test you do ought to mean something. Okay. Now we have an enormous experience with several compounds, particularly chlorhexidine, povidone iodine and, more recently, with Triclosan, PCMX and a few others.

We have a lot of clinical experiences. You heard Dennis this morning talk about reducing the

rate of infection, and his point of view was that one agent was far superior to the other, but the other was effective.

So we do have experience that these things do something that means something. We can't go out and do a clinical trial of, you know, people washing their hands at home, because we have to select populations and show that something happens.

We have a study that was done at enormous expense that shows that you can make a difference in atopic eczema with a modest reduction in bacteria. It had a clinical reduction

We have a lot of data that, I think, a reasonable group of people, some from the FDA. Some people have been doing this kind of thing as a research enterprise for some years, can get together and look at the data and say this is our best analysis in 1998.

As Elaine says, if we need to change it next year, let's have a mechanism so we can change it, instead of having these meetings and then we come back in another two years and we have the same meeting, and

we come back in another two years and we have the same meeting.

CHAIRMAN BRASS: Well, I think what the panel is struggling with is how to take that database that does exist and integrate it into the rulemaking process in a constructive way, so that, for example, if we take the two-tier approach, the agents you have identified would all be antiseptic agents using a variety of criteria, and we could agree on that.

Let's take your example of an agent that was proven efficacious on some clinical endpoint for atopic dermatitis. How does that extrapolate to every American taking a bath in it every night?

DR. LEYDEN: Well, it only extrapolates to them if they have atopic eczema, which --

CHAIRMAN BRASS: That's our point.

DR. LEYDEN: -- about 15 percent of people have.

DR. LARSON: See, that could be the second tier for that application --

CHAIRMAN BRASS: Exactly. That's what we're trying to specify.

DR. LARSON: -- only, and then that product can make the claim for that application, if it's a rigorous, you know, randomized clinical trial, whatever, and then it could have a second tiered claim for that.

DR. LEYDEN: But if the agency -- If the FDA says, okay, here are our people, you know, people from the food, people from the anti-infective division, whatever -- these are the people we think should be involved in this distillation of what information we have, here are the people from industry, here are the other people; get in a room, and don't come out until you have an agreement, you know.

Come to an agreement, and then report it back to a panel like this or to whoever, and disseminate it in the Federal Register and let people comment on it, and then make a decision and say this is what we're going to do, and this is the mechanism to add modifications as modifications become.

Otherwise, we'll be here in ten years, Elaine, and we'll be showing the same slides and

saying the same things.

CHAIRMAN BRASS: Do you have additional comments, Dr. D'Agostino?

DR. D'AGOSTINO: No, no. I'm quite in agreement with this discussion.

CHAIRMAN BRASS: Dr. Neill? Dr. Katz, you wanted to --

DR. KATZ: I just wanted to make one sort of brief aside, is that the current actual indications that are proposed are actually fairly general. Part of the reason why they are so general is so that they would go -- they would encompass a broad spectrum of individuals who might actually use the products.

So that's currently the way it's done right now, just again so that way that something would not be so product specific that we couldn't extrapolate to somebody else.

CHAIRMAN BRASS: Dr. Neill?

DR. NEILL: I'm going to try and answer the questions that you posed to us in that note here, because I think that our role -- I think our role as an advisory committee is to offer --

CHAIRMAN BRASS: This is your first meeting. We try not to follow the directions.

DR. NEILL: It is. Oh, okay. This then is a comment on my suitability, I'll let my comment stand on its own.

You're asking in general terms what are the appropriate tests to reach the performance characteristics. What I've heard is a large minority or even majority -- minority -- of people recommending that clinical trials may be the most appropriate, given the caveat that there are already mechanisms in place to allow for clinical trials to relate to specific additional or tier-two indications or even through the NDA process to get products on the market.

Short of that, I think the criteria that were laid out by you with some modifications by industry seem appropriate. Specifically, in terms of persistence there seems to be a disagreement between the very explicit set of testing that you lay out in this proposal and the desire to include ASTM tests for persistence on the part of industry.

I'm not sure how those tests disagree, how

you're -- you may have drawn specifically from ASTM. I think you make some reference in some of the product persistence tests to ASTM mechanisms, but that seems to me to be the type of disagreement that is the -- you know, ten second versus 15 second, and the thing that people smarter than me are going to have to haggle with and who have a longer life expectancy.

In terms of onset, it seems like there's some agreement about using ASTM. In terms of spectrum of antimicrobial action, it seems like both agree on using some version of MIC.

In terms of activity against resistant versus transient bacteria, some combination of MIC and time kill data; and while there's disagreement about an actual endpoint versus a log reduction and maybe disagreement about the exact starting setting, the methods seem to be in agreement.

One thing that is -- was commented on briefly earlier today, but that concerns me slightly, is that there's not much disagreement about measuring the potential for irritation, because while you propose some standards for measuring this, there

doesn't seem to be in the industry proposal, as I could figure, as specific a way to measure that. Maybe that's just because I'm a bad reader.

The reason that raises a question in my mind is because I'm -- I think I was, you know, ten or 12 when pHisohex was all over the place, and that's what I was supposed to use for my acne, etcetera, and now it doesn't exist, but I'm not sure why.

I believe that that's related to why we're sitting here today, and I'm unfamiliar with the processes that are in place, either FDA or industry, to monitor or provide surveillance data for things like irritation, side effects, etcetera.

I don't know. That's not really a question. Let me put it in the form of a question. No, let me try and get back to answering your question.

I do think it's important to have criteria, a testing criteria that can be stated, whether it's animal based or theory based, model based, whatever, to define what constitutes acceptable levels of irritation, and I think that there ought to

be some sort of agreement about a surveillance system in place, specifically, rather than we'll let the market decide.

Your second question, should testing requirements be based on intended use? Yes. If so, how? It's pretty clear, we don't know.

CHAIRMAN BRASS: Would other radicals like to comment on the specific discussion points?

DR. D'AGOSTINO: A breach of protocol.

CHAIRMAN BRASS: Other comments from anybody? Please? Please identify yourself for the transcriptionist.

DR. SATTAR: I am Syed Sattar from the University of Ottawa in Canada.

Mr. Chairman, my personal view is that even the in vitro testing as specified in the existing version of TFM is perhaps unreasonably stringent or demanding, in the sense that it requires too many strains of bacteria to be tested.

I feel that it is totally uncalled for, because the answer that you will get will really not increase the level of confidence in the end result in

terms of the testing itself.

The concept of using surrogates in terms of microorganisms for testing -- this has now become a fairly accepted practice. If you look at what the other part of FDA does when they deal with high level disinfectants, they use surrogates, one type of mycobacterium of two type of mycobacteria, two types of bacteria spore, and they base their evaluation on the performance of those products as to their activity against the surrogate.

Even in the EPA, when they look at household disinfectants, the concept of surrogates has become a part of the regulatory evaluation process.

So I feel that there are too many bacteria that are required to be tested, and I can't resist the temptation of feeling that the requirements for those many bacteria actually come from an antibiotic mindset, not from a germicide mindset.

I think we should be sensitized to that fact.

CHAIRMAN BRASS: Other comments? Questions?

Well, if not, I'd like to thank very much all the participants for their stimulating and on time discussions, all our discussants, and the panel members, very much.

We are adjourned.

(Whereupon, the foregoing matter went off the record at 3:17 p.m.)

- -

CERTIFICATE

This is to certify that the foregoing transcript in the matter of:

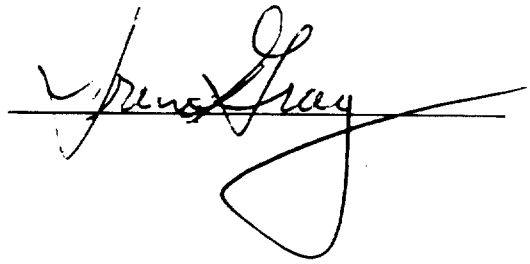
NONPRESCRIPTION DRUGS ADVISORY COMMITTEE meeting

Before: *Department of Health and Human Services*
Public Health Service
Center for Drug Evaluation and Research

Date: July 29, 1998

Place: Bethesda, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.



CERTIFICATE

This is to certify that the foregoing transcript in the matter of:

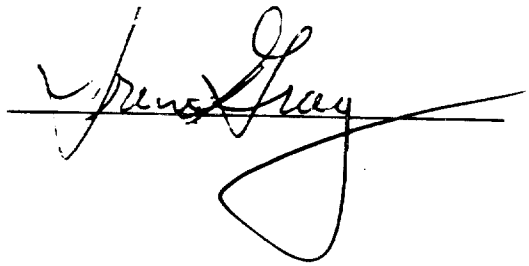
NONPRESCRIPTION DRUGS ADVISORY COMMITTEE meeting

Before: *Department of Health and Human Services*
Public Health Service
Center for Drug Evaluation and Research

Date: July 29, 1998

Place: Bethesda, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.



Look-See Concordance Report

- - -

UNIQUE WORDS: **3,830**
TOTAL OCCURANCES: **19,083**
NOISE WORDS: **385**
TOTAL WORDS IN FILE: **50,016**

- - -

SINGLE FILE CONCORDANCE

- - -

CASE SENSITIVE

- - -

NOISE WORD LIST(S): **NOISE.NOI**

- - -

EXCLUDES OCCURRENCES IN FIRST 3 PAGES

- - -

INCLUDES ALL TEXT OCCURRENCES

- - -

IGNORES PURE NUMBERS

- - -

WORD RANGES @ BOTTOM OF PAGE

– $ –

$100 [1] *144:17*
$120 [1] *200:15*
$3,000 [1] *134:13*

– 1 –

10:27 [1] *106:5*
10:38 [1] *106:6*
12-month [1] *111:15*
12:03 [1] *182:2*
15-second [1] *67:10*
1960s [1] *129:12*
1970s [1] *114:7*
1980s [2] *111:3; 116:9*

– 2 –

20-30 [1] *90:20*
20-time [1] *43:18*
25k [1] *187:1*

– 3 –

30-50 [1] *221:18*
30-second [1] *67:10*
3:17 [1] *297:7*
3M [2] *5:9, 13*

– 6 –

60-second [1] *64:16*

– 7 –

70-80,000 [1] *145:11*
70s [1] *129:12*
73-87 [1] *155:20*

– 8 –

85/95 [1] *194:11*
8:31 [1] *4:2*

– A –

a.m. [3] *4:2; 106:5, 6*
abdomen [1] *257:3*
abdominal [2] *261:15; 262:12*
Abdul [3] *64:8; 183:13, 14*
ability [4] *10:4; 13:2; 92:14; 257:1*
able [25] *11:20; 84:10; 90:14; 107:19; 116:15; 117:1; 150:12; 158:19; 187:22; 189:11; 192:22; 193:3; 194:4, 18, 20; 204:15; 210:4; 245:10; 246:3; 247:8; 252:6; 257:5, 12; 259:8*
absence [4] *35:2; 78:10; 238:21 239:3*
absolute [1] *185:22*
Absolutely [1] *174:21*
absolutely [4] *20:11; 136:8; 234:19; 238:17*
abuse [1] *155:21*
Academy [1] *6:20*
accept [1] *275:7*
acceptable [6] *177:16, 17; 270:20; 271:14; 274:16; 294:21*
acceptance [2] *60:20; 211:5*
Accepted [1] *274:16*
accepted [5] *27:10; 248:3; 274:14; 275:13; 296:4*
access [16] *134:3; 135:3; 136:20; 137:3; 139:11; 140:21; 141:14; 145:16; 146:4; 148:12, 17; 152:5, 9; 210:4; 250:16; 277:12*
accident [1] *285:18*
ACCM [1] *19:13*
according [1] *254:1*
account [4] *138:6, 12; 200:12, 17*
accumulated [2] *105:14; 197:21*
accumulates [1] *92:21*
accurate [1] *76:12*
achieve [9] *17:14; 20:4; 46:12; 52:12; 68:11, 14; 160:13, 14; 209:16*
achieved [4] *69:4, 5; 102:11; 210:21*
achievement [1] *189:10*
acid [3] *164:16, 18; 168:2*
acne [1] *294:7*
acquired [7] *133:11, 15; 147:9; 190:7; 192:16, 20*
acronym [1] *256:18*
act [2] *26:2, 4*
Acting [2] *8:1; 9:1*
acting [7] *11:15; 12:17; 14:15; 26:9, 10, 13; 213:9*
action [9] *23:10, 18; 24:7; 56:13; 165:21; 167:15; 168:6; 259:14; 293:10*
active [7] *49:19; 50:3; 72:15; 73:1, 4, 8; 212:10*
actively [1] *35:12*
activities [4] *80:7; 172:17, 18; 183:10*
Activity [1] *13:1*
activity [30] *10:22; 11:2, 7; 12:19, 20; 24:19; 36:20, 22; 49:3; 50:7; 51:16; 54:15; 55:11; 67:17, 19; 68:7; 84:14, 15; 100:14; 107:3; 143:5; 169:3; 208:1; 248:6, 7; 256:22; 260:1; 293:12; 296:9*
actual [14] *54:20; 116:8; 166:9; 186:22; 235:17; 236:3; 248:18, 20; 254:7; 271:17; 280:9, 22; 291:3; 293:15*
acute [5] *117:22; 144:13; 183:16; 201:14; 202:1*
adapted [2] *44:10; 96:3*
add [17] *217:18; 218:17; 228:3; 246:22; 247:10, 14; 248:16; 251:11; 254:4, 12; 255:10; 260:18; 261:4; 262:17; 264:2; 286:21; 290:20*
Added [1] *160:4*
added [4] *217:11; 222:3; 246:15; 276:2*
adding [2] *257:9; 260:17*
addition [8] *47:16; 49:22; 53:3; 60:19; 61:13; 63:13; 68:3; 200:10*
Additional [1] *69:22*
additional [9] *9:22; 50:16; 60:9; 63:3; 64:21; 218:16; 239:3; 291:2; 292:13*
additive [9] *165:8, 12, 17; 168:8, 12; 170:8, 17; 171:1, 4*
additives [1] *165:16*
address [17] *5:21; 17:10; 18:22; 45:12, 17, 22; 63:22; 100:12; 106:12; 126:8; 134:1; 164:6; 214:21; 228:7; 247:6; 272:7; 284:6*
addressed [9] *27:22; 72:15; 99:12; 168:11; 169:5; 170:19; 235:2; 265:4; 284:22*
addresses [1] *4:10*
addressing [2] *167:19; 226:16*
adds [2] *134:13; 142:11*
Adenoviruses [1] *202:13*
adenoviruses [1] *202:17*
adequate [6] *11:14; 150:1; 160:13; 224:20; 257:15; 283:6*
adhere [1] *247:1*
adjourned [1] *297:5*
administered [3] *38:13; 39:5, 7*
Administration [1] *153:5*
administration [1] *137:3*
admission [2] *60:3; 136:6*
admissions [1] *191:16*
admitted [3] *27:22; 146:14; 190:3*
adopt [2] *161:10; 248:2*
adopted [1] *172:22*
adoption [4] *46:17; 50:10; 124:15, 18*
adult [2] *203:4; 208:18*
advances [1] *133:7*
advantage [2] *34:22; 224:2*
adverse [1] *243:2*
advertised [1] *236:6*
advice [1] *181:10*
advise [1] *258:17*
Advisory [4] *4:5; 7:6, 10, 16*
advisory [2] *272:12; 291:22*
advocates [1] *126:14*
aesthetics [1] *107:4*
affect [4] *51:5; 164:10; 176:7; 187:16*
affected [2] *72:16; 188:3*
affecting [2] *24:12; 200:21*
affiliation [2] *183:9; 185:12*
afford [1] *57:5*
afternoon [3] *144:12; 185:14; 197:4*
AGAR [1] *193:19*
agar [1] *48:20*
age [3] *118:18, 20, 21*
agencies [2] *35:6; 161:10*
agency [13] *4:15; 46:20; 81:18; 240:11; 243:10; 245:18; 264:21; 265:12; 266:7; 284:21; 285:3; 286:17; 290:6*
agenda [3] *4:14; 5:15; 28:22*
agent [24] *85:2; 90:15; 96:21; 110:10; 132:5; 143:22; 145:3, 10; 147:14; 152:7, 13; 158:4, 19; 199:21; 202:1; 216:21; 232:1; 273:17; 274:16; 275:14; 288:2; 289:10*
agents [52] *34:16; 36:22; 42:17; 83:21; 84:13; 97:10; 99:10; 136:14; 143:4; 146:4; 150:3, 17; 151:19, 21; 152:11, 15, 17, 19; 154:12, 13, 17; 155:19; 157:19; 158:21; 159:11; 164:8, 9; 166:18, 20; 167:2, 6, 8; 174:1; 195:6; 197:18; 200:11,*
21; 207:19; 210:7, 10; 211:11; 216:15; 226:19; 232:2; 239:22; 240:1; 268:22; 274:14; 289:7, 8
aggravating [1] *89:5*
agree [27] *23:7; 44:20; 102:15; 109:9; 127:7; 132:7; 144:1; 163:15; 171:16; 177:20; 179:21; 224:3; 228:19; 231:6; 235:5; 246:3; 248:16; 249:20; 253:2; 256:12; 263:11; 264:1; 277:20; 279:4; 285:19; 289:9; 293:10*
agreed [4] *8:22; 9:2; 162:5; 286:1*
agreement [9] *224:19; 226:6; 243:21; 290:13, 15; 291:5; 293:9, 17; 295:1*
agrees [1] *213:21*
agricultural [2] *169:6, 18*
aid [1] *18:6*
aim [1] *196:19*
al [1] *199:17*
alcohol [18] *28:11; 95:17; 108:20; 110:5, 12, 16; 130:14; 141:12, 16; 145:7; 146:6, 18; 147:13; 212:11; 267:13; 279:19*
alcoholic [1] *210:15*
alcohols [4] *109:15; 126:7; 132:17, 19*
alert [1] *121:9*
aligning [1] *26:19*
alive [1] *203:6*
all-important [1] *84:15*
allow [13] *5:1; 47:5; 62:20; 69:6; 100:17; 235:11; 245:18; 246:9; 250:16; 276:7, 12; 286:9; 292:12*
allowed [5] *15:12; 91:3, 4; 195:21; 205:6*

– B –

– C –

– D –

– E –

– F –

– G –

– H –

– I –

– M –

– N –

– O –

– P –

– Q –

– R –

– S –

– T –

– U –

– V –

– W –